Applications of Dihydroarenediols to Chemoenzymatic Synthesis. Approaches to Total Synthesis of Morphine Alkaloids.

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ABSTRACT

The present studies describe, as a primary goal, our recent progess toward the synthesis of morphine alkaloids from aromatic precursors. Model substrates were synthesized which allowed investigation into Diels-Alder, radical cascade, and palladium-catalyzed bond-forming reactions as possible routes to the morphine alkaloid skeleton. As a secondary objective, three separate series of aromatic substrates were subjected to whole-cell oxidation with *Escherichia coli* JM 109 (pDTG601), a recombinant organism over-expressing the enzyme toluene dioxygenase. Included in this study were bromothioanisoles, dibromobenzenes, and cyclopropylbenzene derivatives. The products of oxidation were characterized by chemical conversion to known intermediates. The synthetic utility of one of these bacterial metabolites, derived from oxidation of *o*-dibromobenezene, was demonstrated by chemical conversion to (-)-conduritol E.

LIST OF ABBREVIATIONS

Ac	Acetyl
AIBN	2,2′-Azoisobutyronitrile
Bn	Benzyl
BTIB	*bis*-(Trifluoroacetoxy)iodobenzene
Bz	Benzoyl
COSY	(proton) Correlated spectroscopy
CSA	Camphorsulfonic acid
DBS	Dibenzylsuberylamine
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DMAP	Dimethylamino pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	2,2-Dimethoxypropane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
Dppf	1,1′-*Bis*-(diphenylphosphino)ferrocene
EDC	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride

HRMS	High resolution mass spectrometry
HMPA	Hexamethylphosphoramide
IMDAF	Intramolecular Diels-Alder reactions of Furan
Imid	Imidazole
IR	Infrared
ISP	Iron-sulfur protein
KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminum hydride
*m*CPBA	*m*-Chloroperoxybenzoic acid
NAD	Nicotinamide adenine dinucleotide
NBS	*N*-Bromosuccinimide
NMO	*N*-methyl-morpholine-*N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
PAD	Potassium azodicarboxylate
PCC	Pyridinium chlorochromate
Pd	Palladium
PMA	Phosphomolybdic acid
Py	Pyridine
TBAF	Tetrabutylammonium fluoride
TBS-Cl	*t*-Butyldimethylsilyl chloride
TBS-OTf	Tributyldimethylsilyl triflate
TDO	Toluene dioxygenase

TEA	Triethylamine
TEBAC	Benzyltriethylammonium chloride
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THS-Cl	Dimethylthexylsilyl chloride
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TsCl	Tosyl chloride

I. Introduction

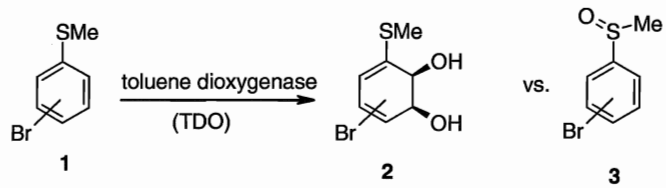
The formation of chemical bonds with complete regio- and stereochemical control is becoming a paradigm in organic synthesis. Enzymes, nature's chemical catalysts, are recognized for their ability to perform chemical transformations with extraordinarily high levels of stereo- and chemoselectivity. Several enzymatic reactions are amenable to scalable synthetic applications, including Baeyer-Villiger Monooxygenases (used in the synthesis of chiral lactones), fungal enzymes (known to hydroxylate a wide variety of substrates), dioxygenase enzymes (which install two oxygen atoms into their substrate), and lipases, which may be utilized either as a highly-selective acylation catalyst, or most often, in resolution of alcohols by intermediacy of their ester precursors. With increased restrictions on waste generation, industrial chemists continue to seek out more environmentally benign methods of chemical transformation. As most enzymatic reactions require aqueous conditions, the problem of organic waste disposal is reduced for such reactions.

Oxidations of aromatic compounds by prokaryotic organisms represent an important class of enzymatic reactions.The research in the Hudlicky group is directed at the synthesis of natural products and their derivatives using starting materials which are generated by enzymatic transformations. In 1968, Professor David Gibson (University of Iowa) reported the isolation of *Pseudomonas putida*, a soil bacterium which utilized ethylbenzene or toluene as its sole source of carbon and energy.[1] Gibson's research into the catabolic pathways of this organism led to his isolation of a mutant strain, *Pseudomonas putida* F1, which converted arenes to their homochiral cyclohexadiene-cis-1,2-diols. In 1989, Gibson reported the construction of a genetically engineered

Escherichia coli organism which provided synthetically useful amounts of the metabolites from fermentation.[2] Since the time of Gibsons's 1968 publication, over 300 dienediol metabolites have been reported. The homochiral diol metabolites isolated from whole-cell fermentation of halobenzenes with *Escherichia coli* JM 109 (pDTG601) have been employed in a variety of enantioselective syntheses. We are engaged in a program directed at the isolation of new metabolites with emphasis on their application in the enantioselective synthesis of complex target molecules. New directions in this area include studies on the oxidation of aromatic sulfur-containing compounds and aromatic compounds bearing an asymmetric center proximal to the site of oxidation.

In addition to the provision of more elaborate compounds for synthetic utility, the present study provides a more complete picture of the mechanism of oxidation, which has yet to be elucidated. It has been known for some time that the enzyme toluene dioxygenase is highly promiscuous, that is, it exhibits a low specificity for its natural substrate, toluene. Promiscuous enzymes are of some import to the synthetic community because such enzymes often have the ability to accept and transform hundreds of different compounds with a variety of functional content and substitution.

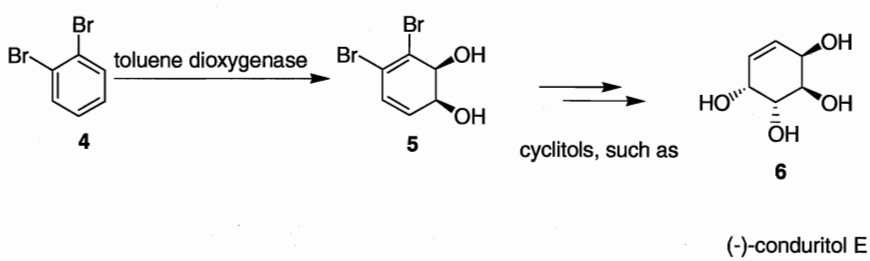
A significant part of the present study is devoted to the isolation and characterization of new enzymatic metabolites. In particular, we consider the oxidation of a series of bromo-thioanisoles, Figure 1. It will be shown that (1) the enzyme toluene dioxygenase is capable of carrying out selective oxidations of halo-thioanisoles at sulfur, yielding in many cases (*R*)-sulfoxides, and (2) the outcome of oxidation is (sulfur oxidation vs. ring oxidation) is highly influenced by the substitution patterns on the ring.



1 2 3

Figure 1. Oxidation of thioanisoles to give dienediols or chiral sulfoxides.

Previously, the dienediol derived from *m*-dibromobenzene had been employed in the synthesis of narciclasine by Hudlicky and co-workers.[3] Although very few *m*-substituted aromatics are known to be good substrates for the enzyme toluene dioxygenase, this particular metabolite is an exception because of its inherent plane of symmetry. The results of whole-cell fermentations with the remaining members of this series of dibromobenzenes, the meta- and ortho-isomers, will be presented and discussed with regard to their symmetries. The potential for broad application of these metabolites to the synthesis of cyclitols will be presented.



4 5 6

Figure 2. Projected synthesis of cyclitols from *o*-dibromobenzene.

The metabolites from fermentation, such as **5** may be converted to cyclitols or aminocyclitols through epoxidation or aziridination reactions, respectively. The selective opening of either epoxides or aziridines allows for a programmed approach to the synthesis of cyclitols, aminocyclitols, or their unnatural derivatives. A general study of

the application of silica gel as a mild catalyst for the opening of vinyl aziridine and vinyl epoxides is presented.

One question that has yet to be completely answered is whether the enzyme is capable of resolving racemic centers proximal to the site of oxidation, and if so, what structural requirements must these substrates exhibit in order to effect chiral resolution. We will study the outcomes of such oxidation reactions by preparing several racemic aromatic cyclopropanes, which will be subjected to enzymatic oxidation as shown in Figure 3.

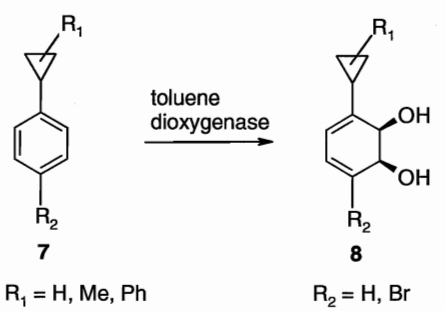


Figure 3.

The outcome of these substrate specificity studies will strengthen Boyd's[4] hypothesis that it is the larger substituent on the aromatic ring which influences the outcome of oxidation on the ring.

Our interest in aromatic and sulfur oxidations combined with our long-standing involvement in morphine synthesis allows the implementation of a thiophene-oxide/ Diels-Alder strategy toward thebaine. The key step in this new approach would rely on a tandem thiophene oxidation followed by trapping of the thiophene oxide with an intramolecular olefin tether. The approach is based on several reports of thiophene derivatives undergoing enzymatic or chemical oxidations at sulfur. The oxidation, which destroys aromaticity in the heteraromatic nucleus, unmasks a reactive latent diene in the

form of the heterocycle. The results of our efforts in this approach are presented in Chapter III-6.8.

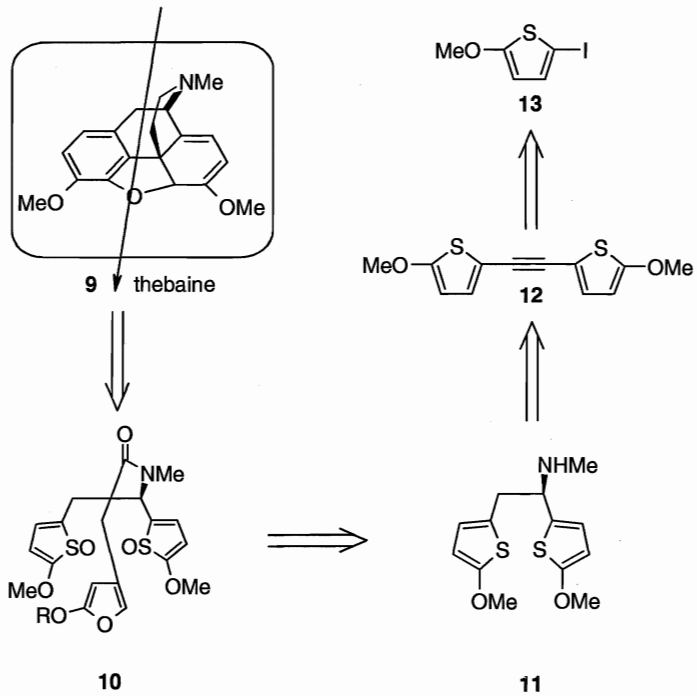


Figure 4. Retrosynthetic analysis of thebaine synthesis.

Finally, several chemoenzymatic approaches to the synthesis of morphine will be presented. The Heck reaction, used in Overman's,[5] Trost's,[6] and Hudlicky's[7] morphinan synthesis to establish the C-13 quaternary center, was re-visited in a series of model substrates-all of which were derived from fermentation. A second approach, which also features palladium catalysis, would allow the introduction of the aromatic A-ring portion to the C-ring by means of allylic acetate displacement chemistry developed in Trost's laboratories. The results of a detailed study of these reactions in addition to future directions for morphine synthesis are described.

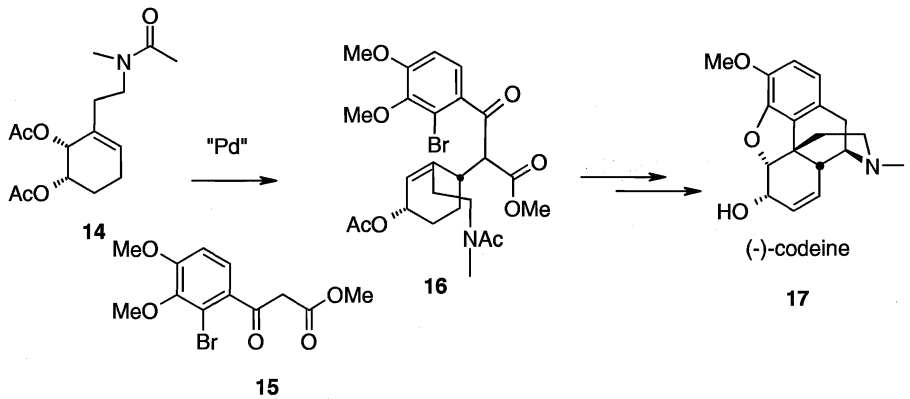


Figure 5.

Since its first reported total synthesis a little more than a half century ago, morphine remains a considerable challenge to the synthetic chemist. There have been just under thirty formal or total syntheses of the natural product; each of these strategies is unique in addressing the issues of complexity. The introduction of asymmetry in the starting material represents a key step in the synthesis of Gates', Trost's, Overman's, and Parker's non-racemic syntheses of morphine, or its derivatives. Hudlicky's approach is unique in that chirality in the starting material is generated through enzymatic methods. A brief account of the historical development of this chemistry is described in the following section. The design elements and key steps of a selected number of total syntheses featuring Diels-Alder, radical cyclizations, or Pd-catalyzed cyclizations will be discussed in Chapter 3.

II. Historical

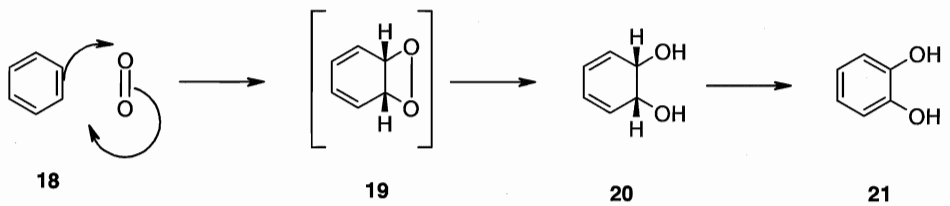
II-1 Aromatic Dioxygenases

II-1.1 History of Microbial Oxidation of Aromatics

As early as 1908, Störmer isolated a bacterium, *Bacillus hexcarbavorum*, which utilized toluene and xylene for growth.[8] Several years later, in 1913, Söhngen described microorganisms which grew in the presence of benzene.[9] Subsequent studies by Haccius and Helfrich[10] with the organism *Nocardia coralline* determined that catechol was the major product from the fermentation of benzene. These, and other, early reports generated significant interest in both the specificity of microbes for various substrates, and the mechanisms of such oxidations. At the time, there was some question of whether or not the catechol was formed through the intermediacy of phenol, or rather through oxidation of an aromatic diol. An elegant study by Marr and Stone[11] using *P. aeruginosa* and *Mycobacterium rhodochrous*, which were isolated from soil samples, showed that both strains oxidized benzene to catechol. The organisms were capable of growing solely on catechol as well, but not in the prescence of phenol, which led them to discount phenol as an intermediate in the degradive pathway of benzene. Although they were unable to isolate the *trans*-cyclohexa-3,5-diene-1,2-diol as an intermediate, Marr and Stone nonetheless proposed its intermediate role in the formation of catechol from benzene based on analogy to eukaryotic organisms which were reported to oxidize *trans*-cyclohexa-3,5-diene-1,2-diol to catechol.

In 1968, Gibson, Kallio, and Koch reported a strain of *Pseudomonas putida* that utilized ethylbenzene, toluene, or benzene as its source of carbon.[1] They found that the

cell-extracts from the organism oxidized these aromatic hydrocarbons at equal rates. They performed oxygen uptake experiments in which the organism was incubated with both *cis*- and *trans*-cyclohexa-3,5-diene-1,2-diols. These experiments revealed that the *cis*-isomer was oxidized approximately 6 times faster than its *trans*-isomer. The result of this experiment, combined with their inability to detect phenol as an intermediate in the pathway led to the initial mechanistic proposal depicted in Scheme 1.



Scheme 1. Gibson's original mechanistic proposal for dihydroxylation of benzene.

II-1.2 On the Mechanism and Stereochemistry of Aromatic Oxidation

In 1970, Gibson extended his work on aromatic oxidations by *Pseudomonas putida* to include halogenated aromatic derivatives. He reasoned that, because of the deactivating nature of the halogen substituent, metabolism may be retarded such that the intermediate compounds in the degradive pathway may be isolated and characterized. Indeed, Gibson found that oxidation of toluene, fluoro-, chloro-, bromo-, and iodobenzene gave the corresponding *m*-substituted catechols. The oxidation of *p*-chlorotoluene **22**, however, gave a mixture of the 2,3-dihydroarene diol **23** and the corresponding catechol **24**, Figure 6. On the basis of Crigee's triacetylosmate test and NMR spectroscopic evidence, Gibson was confident that he had originally been correct in postulating the existence of a 1,2-cis-diol intermediate.

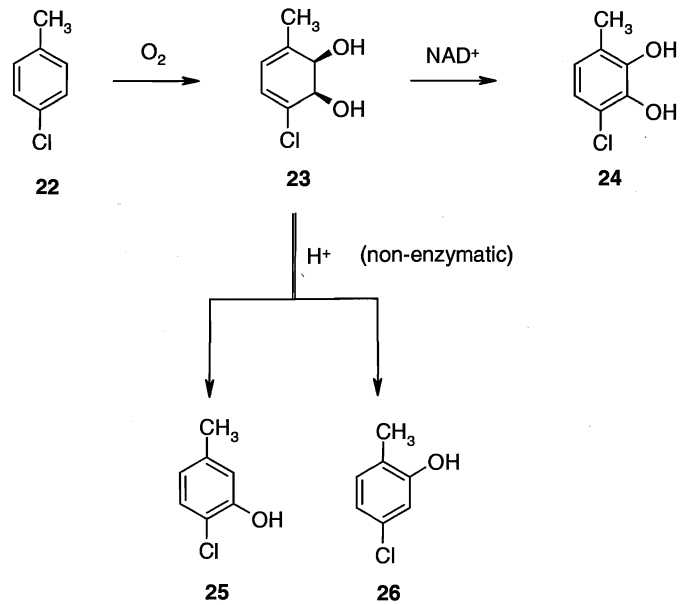


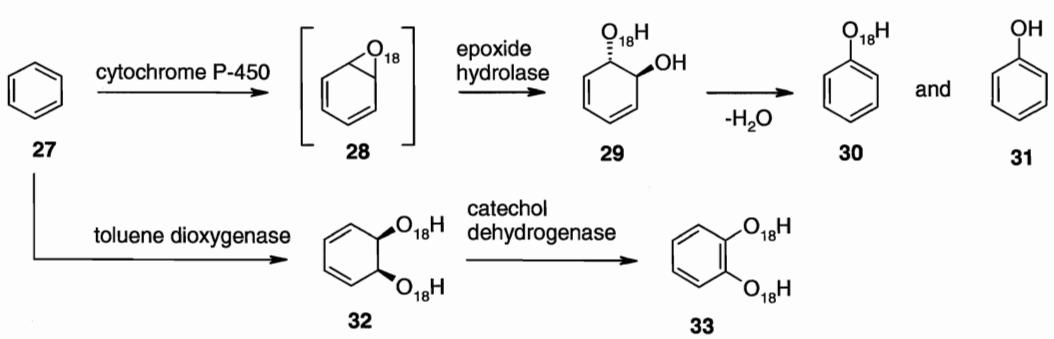
Figure 6. Gibson's isolation of intermediates in aromatic degradation.

The proof of stereochemistry for the dienediol derived from oxidation of toluene was reported in 1973. [12] The proof involved hydrogenation of (+)-*cis*-1,2-dihydroxy-3-methylcyclohexa-3,5-diene, and further oxidation under Jones conditions to the corresponding di-acid. Upon comparison of this material to the known (-)-2-(*R*)-methyladipic acid, they reported an unambiguous stereochemical assignment of the cis-diol. This particular experiment, however, only permits an absolute stereochemical assignment of the methyl group. The authors assume that hydrogenation occurs from the α-face of the molecule, which was later shown to be the predominant, but not exclusive, pathway.[13] The absolute proof of the absolute configuration had to await the synthesis of $PGE_{2\alpha}$ in 1988.[13]

Mechanistic studies aimed at elucidation of the pathways for the formation of diols and catechols from aromatic precursors had constituted an active area of research since the early 1950's. A study by Booth, et al. in 1960 involved the incubation of either

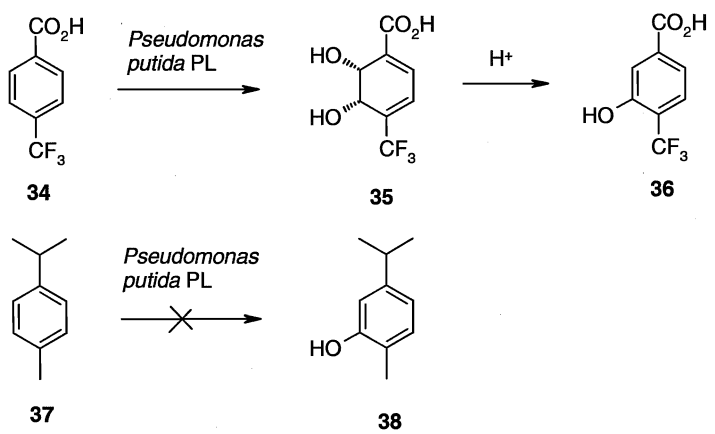
benzene or naphthalene with NADPH, $^{18}O_2$, and rat liver microsomes.[14] Under these conditions, aromatic substrates showed incorporation of only one labeled atom of oxygen, implying the intermediacy of an epoxide, which is opened in a *trans*-diaxial fashion to give *trans*-1,2-diols. In a seminal 1970 paper,[15] Gibson proved unambiguously through isotopic labeling studies that *both* oxygen atoms present in the cis-diol functionality are derived from molecular oxygen. At this point, it became clear that the mechanisms for oxidation of aromatics compounds in microbes differed from those in mammalian systems.

Cytochrome P-450's, the broad class of hydroxylating enzymes common to mammalial organisms, are known to oxidize aromatics to catechols via their epoxide intermediates, Scheme 2.[16] The intermediate epoxide may be hydrolyzed to its *trans*-1,2-diol, an unstable intermediate which undergoes dehydration to give phenol. Dioxygenase enzymes[17] characteristically incorporate two oxygen atoms into their substrate, in the case of toluene dioxygenase, molecular oxygen serves this function. Re-aromatization occurs not as a result of dehydration, but rather by further oxidation mediated by a second enzyme, catechol dehydrogenase.



Scheme 2. Divergent modes of oxidation for cytochrome P450 and dioxygenases.

Independent of Gibson, Ribbons and co-workers were investigating the pathway by which *p*-cumene **37** (4-isopropyltoluene) was degraded by *Pseudomonas* strains.[18] They found that co-incubation of wild-type *Pseudomonas putida* PL, known to oxidize *p*-cumene to its catechol, with cumene in the presence of 4-halotoluenes resulted in the accumulation of appreciable amounts of the intermediate 2,3-dihydroarenediol intermediate derived from the halotoluene additive. Furthermore, they were unable to detect the products arising from oxidation of cumene. They concluded that the production of the intermediate halo-aromatic diol was the result of the prescence of mutant strains of *Pseudomonas* that were unable to grow in the prescence of *p*-cumene, Scheme 3. Such additives which are enzymatically processed to compounds which interfere with metabolic pathways have been termed "suicide compounds".[19]



Scheme 3. Co-incubation of *Pseudomonas putida* P1 with halo-toluenes results in formation of mutants strains.

Gibson was also interested in generation of mutant strains of bacteria responsible for the catabolism of aromatics. By incubation of the wild strain of *Pseudomonas putida* with *N*-methyl-*N*-nitrosoguanidine, he was able to generate mutant strains of the parent organism. His work led to the isolation and characterization of a mutant strain, which he

named *Pseudomonas putida* F39D, devoid of the ability to carry out oxidation of the intermediate dihydroarene diol. Incubation of this mutant organism with ethylbenzene or toluene resulted in the accumulation of the cis-dihydroaromatic diol. Following characterization of the mutants, the genes responsible for the production of toluene dioxygenase were eventually expressed in *Escherichia coli.*[20] Dioxygenase enzymes produced by *Pseudomonas putida*, the soil bacteria which carry out these transformations, are part of a catabolic pathway by which aromatics are degraded to acetate- a source of carbon and energy for the organism. The transformations which define this catabolic pathway are detailed in Figure 7.

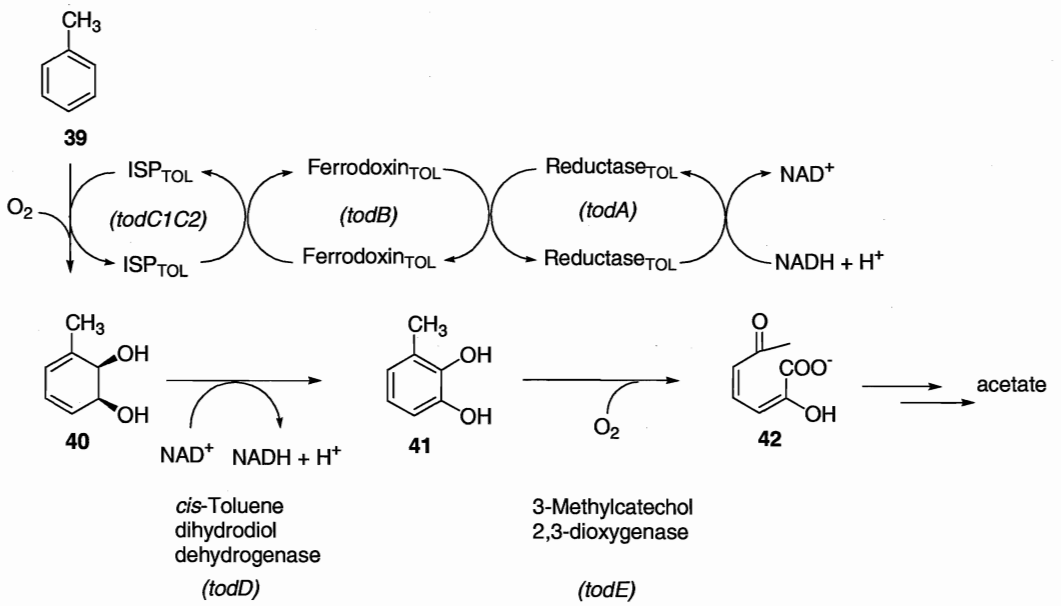


Figure 7. Catabolism of toluene in soil bacteria. Gene designations are shown in parentheses.

Electron transport from NADH is facilitated by a reductase protein, which shuttles electrons to a ferrodoxin protein, which in turn reduces an iron-sulfur protein. The iron sulfur protein (ISP_{TOL}) reduces molecular oxygen, which is incorporated with cis-

stereochemistry into the aromatic substrate with concomitant loss of aromaticity. In the wild-type organism, cis-dihydrodienediol **40** undergoes an NADH-mediated oxidation to its corresponding catechol **41** by the enzyme *cis*-toluene dihydrodiol dehydrogenase. The action of a second dioxygenase enzyme, 3-methylcatechol 2,3-dioxygenase, is responsible for the conversion of the catechol to 6-oxo-2,4-heptadienoate **42**.

The nucleotide sequence of the toluene dioxygenase genes, elucidated through isolation and characterization of the mutant strains, was reported in 1989 by Gibson and Zylstra.[2] These genes were actively expressed in an *Escherichia coli* host. Even after the genes had been cloned into *E. coli* (a significant feat given the length of the nucleotide sequence and complexity of the enzyme system) there is continued interest in the study of toluene dioxygenase and its related dioxygenases. The exact mechanism of the oxidation of aromatic substrates by toluene dioxygenase remains unknown, although X-ray crystal data of a related dioxygenase enzyme, that of naphthalene dioxygenase, is available.[21]

There are several advantages associated with the use of recombinant strains of *E. coli* over the mutant strains. Mutant strains require an aromatic inducer of protein production, normally chlorobenzene or toluene. As the inducer is itself a substrate, difficulties are encountered in the purification of novel substrates. Enzyme production in the recombinant organism, however, is initiated by a sugar analogue, *β*-isopropylthiogalactopyranoside, obviating the need for addition of an aromatic inducer. Second, recombinant cells contain multiple copies of the plasmid, resulting in increased production of the protein and hence increased yields of diols.

Nearly forty years after Gibson's isolation of the first stable cis-cyclohexadienediol, there is continued interest in the application of these unique synthons

in both natural products and materials chemistry. The dihydroxylating enzymes responsible for the stereospecific installation of the cis-diol functionality to aromatic nuclei with concomitant loss of aromaticity are unique to the world of enzymatic transformations- there is as yet no equivalent reaction in standard reagent chemistry. One exception is an attempt from Motherwell,[22] who described a photochemically-mediated oxidation of benzene, however, this oxidation is non-selective and is limited to benzene.

II-1.3 Utility of Dioxygenase Enzymes in Synthesis

It is remarkable that the evolution of the process from Gibson's discovery of the first stable cis-dihydrodiol to industrial scale (>1000 L) production of cis-dihydrodiol has taken less than forty years. The products derived from microbial dearomatization of aromatics are ideal substrates for the synthesis of a variety of complex natural products and analogues. Not only are the products formed in homochiral fashion, but also, all six carbon atoms in the molecule all susceptible to selective functionalization. The olefins are sterically and electronically differentiated and the diene functionality can be utilized in intra- or intermolecular Diels-Alder reactions. The cis-diol functionality provides an anchoring point for a variety of functional tethers, or may be exploited as a directing element in enantioselective chemical reactions, as indicated in Figure 8. Indeed, there is enormous potential for application of these diverse dihydroarenediols in synthesis. Since Gibson's original paper describing the oxidation of arenes by *Pseudomonas putida*,[1] over 300 metabolites have since been reported. It is remarkable that twenty years had passed from the isolation of the first arene diol before the synthetic potential of these metabolites had materialized.

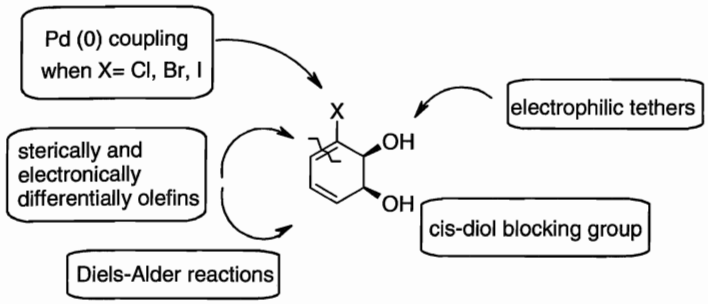
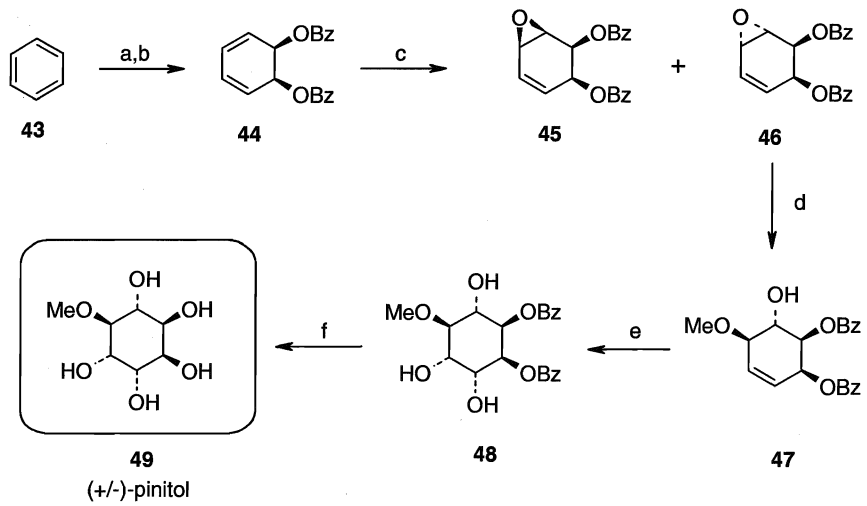


Figure 8. Reactive options in diene diols.

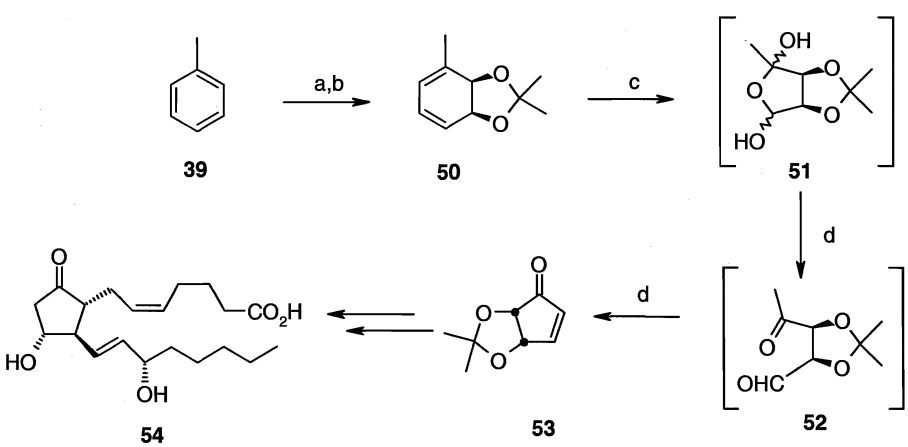
The first application of cis-dihydrodiols in a synthetic endeavor is credited to Ley, whose synthesis of racemic pinitol was reported in 1987.[23] Ley's synthesis begins with benzene, which was converted enzymatically to its meso-diol using the mutant strain of *Pseudomonas putida* F1, a bacterial strain expressing the enzyme toluene dioxygenase and is devoid of the enzyme catechol dehydrogenase. The meso-diol was protected as its bis-benzoate derivative **44** and the benzoates subjected to epoxidation with *m*CPBA. At this stage of the synthesis, the mixture of epoxides **45** and **46** were easily separated by column chromatography and the desired α-epoxide **46** opened with methanol in the presence of camphor sulfonic acid. Osmium-mediated dihydroxylation gave the fully-oxygenated derivative **48**, which was deprotected by treatment with aqueous methanol in the presence of triethylamine to afford racemic pinitol **49**.



Reagents and Conditions: (a) *Pseudomonas putita* F1; (b) PhCOCl, DMAP, py; (c) *m*CPBA, DCE, pH 8 phosphate buffer; (d) MeOH, CSA; (e) 0.1% OsO_4, NMO, *t*BuOH/THF/H_2O; (f) Et_3N, MeOH, H_2O.

Scheme 4. Ley's synthesis of racemic pinitol.

Just one year later, the chirality in the enzymatically-generated dienediol was exploited in the synthesis of prostaglandin intermediates and perhydroazulene terpenes by Hudlicky and co-workers.[13] The synthesis is noteworthy as it marked the first enantioselective synthesis using dihydroarene diols.



Reagents and Conditions: (a) *Pseudomonas putita* 39D (3 g/L); (b) 2,2-dimethoxypropane, *p*TsOH, rt (85%); (c) O_2/O_3, then dimethyl sulfide (56%); (d) neutral alumina, DME, reflux, 15 min (95%).

Scheme 5. Hudlicky's chemoenzymatic preparation of prostanoid synthon **53**.

As depicted in Scheme 5, *Pseudomonas putida* 39D, a mutant strain which expresses the enzyme toluene dioxygenase, was used to oxidize toluene to its aromatic diol, which was immediately protected as an acetonide **50**. Treatment of this material with ozone provided the isomeric mixture of hemiaminal **51**. Heating the mixture in DME in the presence of neutral alumina gave directly the α,β-unsaturated ketone **52**, which had previously been converted to prostagladins,[24] thus completing a formal synthesis of $PGE_2\alpha$ from toluene in four operations.

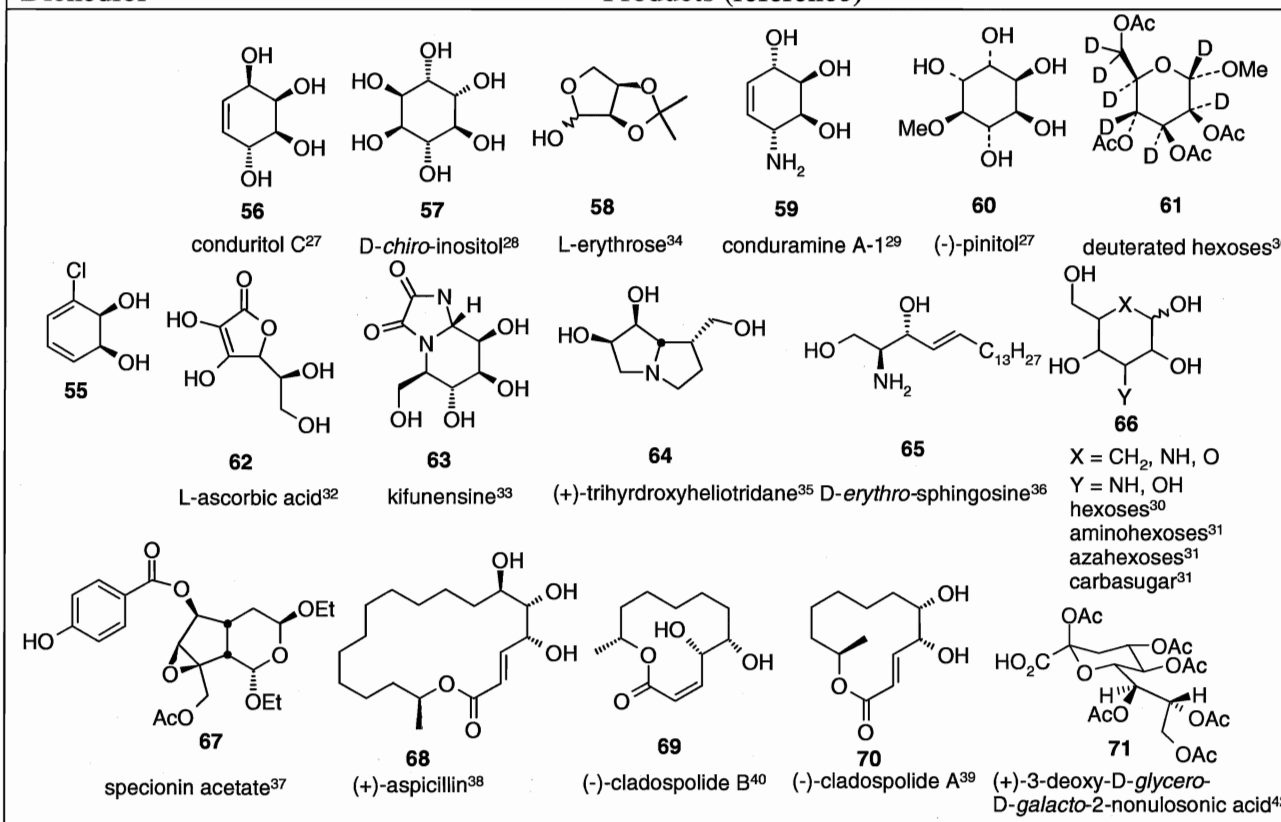
Nearly 20 years have passed since Ley's first report of the application of dienediols in synthesis. Since 1987, over 50 natural products and derivatives have been synthesized from diene diols obtained by fermentation of aromatics.[25] Although over 300 metabolites are known, nearly 70% of all the natural products originating from aromatic nuclei were synthesized from either benzene, chlorobenzene, toluene, or bromobenzene. The synthetic utility of the remaining 300 metabolites is yet a largely unexplored area of research. A summary of some of the synthetic targets derived from aromatic diols is given in Table 1 below. Several excellent reviews are devoted to the application of diene diols in synthesis.[26] Chlorobenzene served as starting material in the synthesis of conduritol C,[27] D-*chiro*-inositol,[28] conduramine A-1,[29] (-)-pinitol,[27] hexoses,[30] aminohexoses,[31] and carbasugars,[31] L-ascorbic acid,[32] kifunensine,[33] both D- and L-erythrose,[34] both enantiomers of trihydroxyheliotridanes,[35] natural and unnatural sphingosines,[36] specionin acetate,[37] (+)-aspicillin,[38] (-)-cladospolide A,[39]cladospolide B,[40] and the isomeric D-*chiro*, L-*chiro*, *muco*-, *neo*-, and *allo*-inositols,[41] and 3-deoxy-D-glycero-D-galacto-2-nonulosonic acid.[42] Bromodienediol has witnessed application in the synthesis of pancratistatin,[43] 7-deoxypancratistatin,[44] and truncated[45] and modified

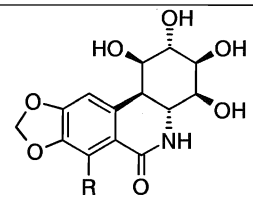
aromatic[46,47,48] derivatives of the pancratistatin core. It has been used in the synthesis of lycoricidine[49], amino-inositols,[50] *ent*-bengamide E,[51] morphinans,[52] the core of CP-225,917,[53] steroidal nuclei,[54] and aza-disaccharides,[55] chiral polymers,[56] and a host of conduritols and conduramines.[57] (-)-Gabosine remains the only target which has been made through the intermediacy of iodobenzene dihydrodiol.[58] The diol derived from toluene was one of the first to find application in total synthesis. It has been used to make (-)-patchoulenone,[59] the *ent*-taxane A,B ring system,[60] mannose derivatives,[61] $PGE_2\alpha$,[13] morphinan ring systems,[62] and hirsutene.[63] Styrenedienediol has provided access to zeylena[64] and structurally complex Diels-Alder adducts.[65] Bromoethylbenzene diol has been used in approaches to natural morphinans,[66] while its corresponding *o*-bromo isomer was used as an intermediate in the synthesis of isoquinoline derivatives which were ultimately converted to *ent*-morphinans.[67] Shkimic acid was synthesized from benzenenitrile.[68] *m*-Dibromobenzene served as starting material for the synthesis of narciclasine,[3] and its corresponding *o*-isomer was recently converted to (-)-conduritol E.[69] The protesase inhibitor indinivir (Crixivan) was synthesized from the diol biocatalytically derived from indane.[70] (+)-Goniodiol was recently prepared from naphthalene diendiol by Banwell and co-workers.[71] *p*-Bromoiodo dienediol was used to make *ent*-7-deoxypancratistatin.[44] The diene derived from oxidation of azidoethylbenzene was used in the synthesis of truncated morphinans.[62] The diol derived from benzene has been converted to either enantiomer of conduritol C,[72] both enantiomers of methyl shkimate,[73] and polyphenylene.[74] Indole was biocatalytically converted to indigo.[75]

Table 1. Examples of Natural Products and Materials Derived from Aromatic Diols.

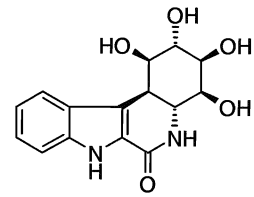
A. Asymmetric Syntheses

Dienediol	Products (reference)

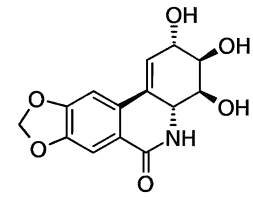




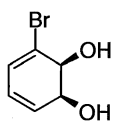
73 R = OH pancratistatin[43]
74 R = H 7-deoxypancratistatin[44]



75
B-carboline-1-one mimic[47]



76
lycoricidine[49]



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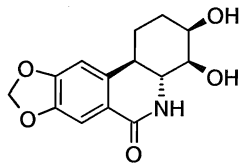
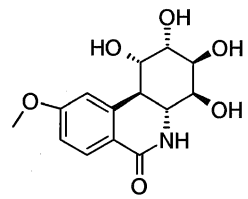
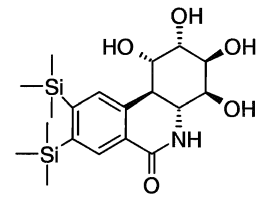
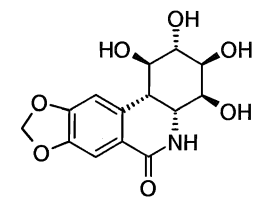
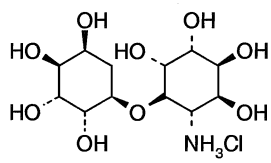




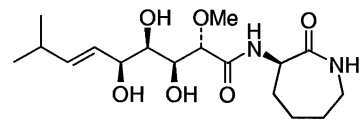




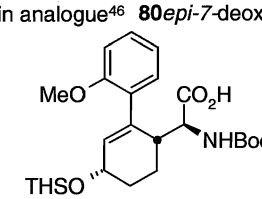
77 pancratistatin analogue[45] **78** pancratistatin analogue[45] **79** pancratistatin analogue[46] **80***epi-7*-deoxy pancratistatin[48]



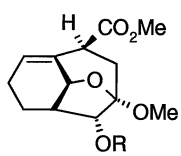
81
amino-inositol dimer[50]



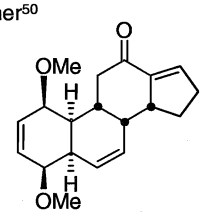
82
ent-bengamide E[51]



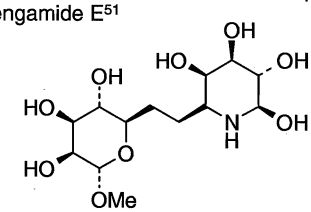
83
morphinan[52]



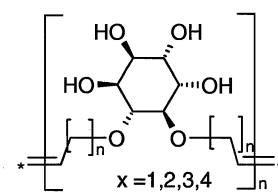
84
core of CP-225,917[53]



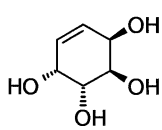
85
steroidal nuclei[54]



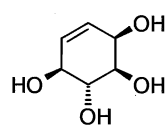
86
aza-C-disaccaride[55]



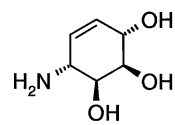
87
chiral polymers[56]



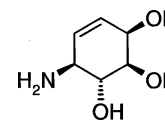
6
(-)-conduritol E[57]



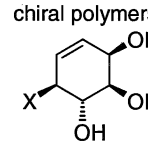
88
(-)-conduritol F[57]



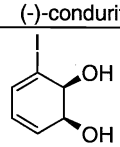
89
conduramine A-1[57]



90
conduramine F-4[57]



91
X = F, Cl
deoxyhalo-conduritols F[57]



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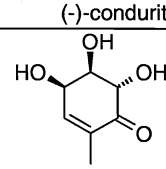
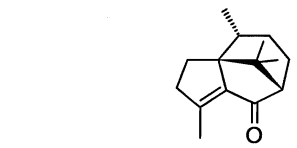
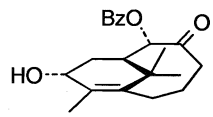


93
(-)-gabosine A[58]



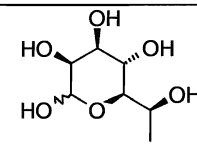
94

(-)-patchoulenone[59]



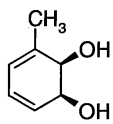
95

ent-taxoids AB-ring system[60]



96

6*C*-methyl-D-mannose[61]



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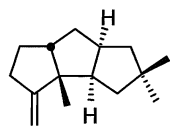
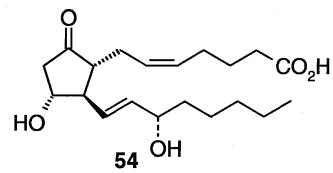


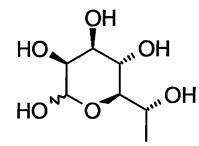
97

(+)-hirsutene[63]



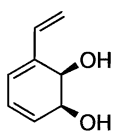
54

PGE_{2alpha}[13]



98

6*C*-methyl-D-mannose[61]



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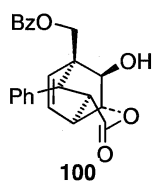
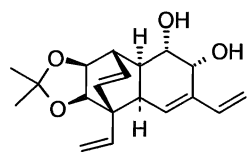


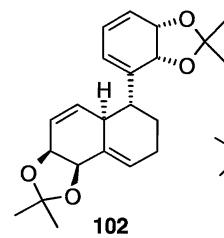
100

zeylena[64]



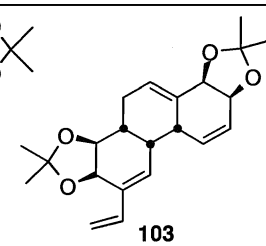
101

Diels-Alder adduct[65]



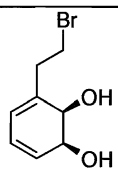
102

Diels-Alder adduct[65]



103

Diels-Alder adduct[65]



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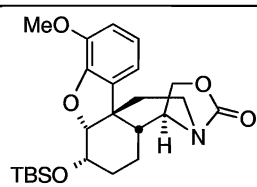
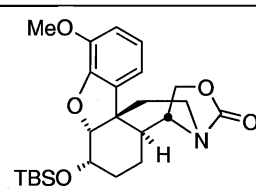


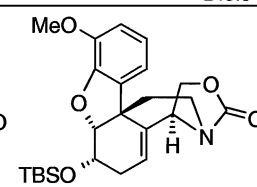
105

morphinan[66]



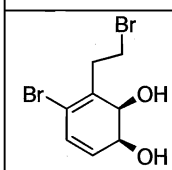
106

morphinan[66]



107

morphinan[7]



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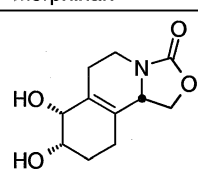
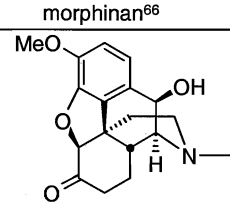


109

isoquinoline derivative[67]



110

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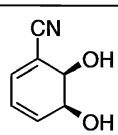

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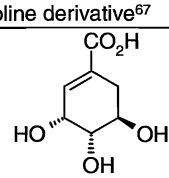

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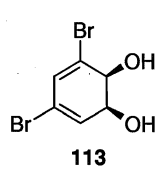

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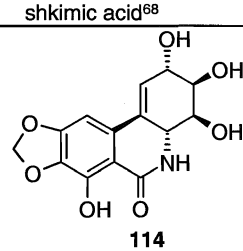
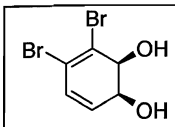


114

narciclasine[3]



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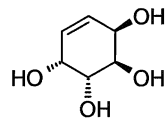
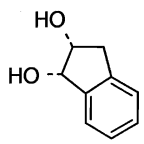


6

(-)- conduritol E[69]



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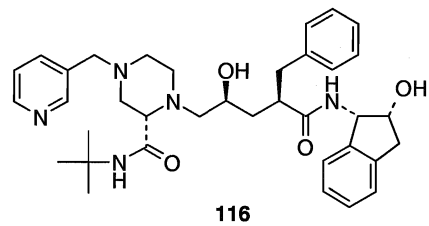
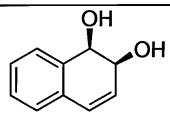


116

indinivir (Crixavan)[70]



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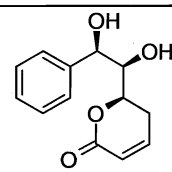

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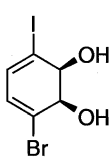

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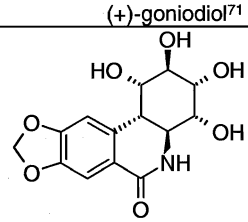

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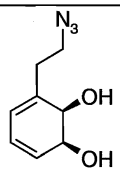
ent-7-deoxypancratistatin[44]



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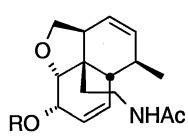
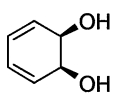


122

morphinan[62]

B. Non-asymmetric syntheses[a]



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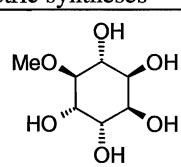

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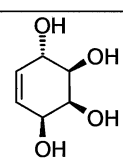
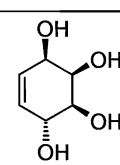
(+/-)-pinitol[23]



124

(+)-conduritol C[72]



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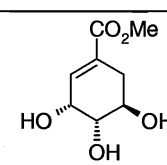
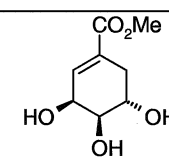


125

(-)-methyl shikimate[73]



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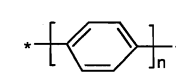
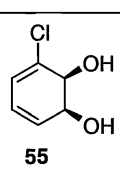
(+)-methyl shikimate[73]



127

polyphenylene[74]



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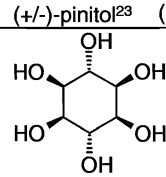
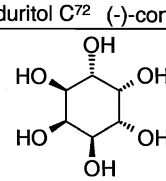


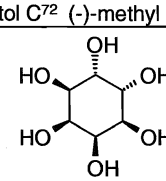
128

muco-inositol[41]



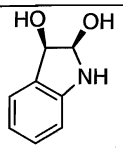
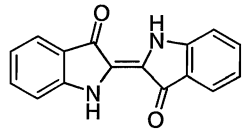
129

neo-inositol[41]



130

allo-inositol[41]

 **131**	 **132** indigo[75]

[a]Syntheses in which either the product is devoid of chirality, or if the product is chiral, asymmetry was introduced by some means to the *meso*-diol.

Recent advances in biotechnology have allowed access to synthetically useful amounts of a variety of diols derived from aromatic nuclei. The the utility of dienediols in asymmetric synthesis is clearly demonstrated by entries in Table 1. The diversity of the metabolites shown in Table 1 is a testament to the high degree of tolerance of the enzyme for both molecular shape and functional content in the aromatic substrate. There are, no doubt, hundreds of metabolites that have yet to be isolated.

The metabolites derived from halobenzenes are especially amenable to further functionalization and they have seen broad application in Diels-Alder chemistry,[37,38] Pd-catalyzed coupling reactions,[49,66a] ozonolysis,[13] hydroxylation,[41] and or, epoxidation[41] reactions. While these substrates traditionally find application in the synthesis of natural products, recently there have been a growing number of reports describing their usage in the synthesis of non-natural medicinal agents, i.e. indinivir, chiral polymers, and colorants (indigo). The growing number of substrates isolated from whole-cell fermentation of aromatics bodes well for the field of chemo-enzymatic synthesis.

As demonstrated in Ley's synthesis of pinitol, dienediols are excellent substrates for further selective oxidation reactions. On closer inspection, many of the targets illustrated in Table 1 which retain an oxygenated core can be dissected into amino-cyclitol or cyclitol fragments. A significant number of these natural products and

materials result from an initial coupling of either epoxide or aziridine scaffolds with various nucleophiles. To this end, there is significant research devoted to the development of operationally simple, selective, and mild, catalytic systems to facilitate opening of these functional synthetic intermediates. The following section presents the use of silica gel as a mild alternative to acid or metal catalytic systems.

II-2 Reactions on Silica Surface

The rate enhancement and increased reactivity of many reactions on solid surfaces is well-established. [13,47,76,77] Because of their extremely large surface area, solid phase catalysts such as alumina, zeolites, and silica provide an enormous contact surface which necessarily distributes reactants in a proximal arrangement, thereby lowering the reaction activation energy. This phenomenon has been exploited in a number of diverse applications from polyolefin polymerization[78] to Diels-Alder and ene-reactions.[79] Additionally, increasing demands for catalysts which are recyclable, non-toxic, and of low cost have prompted many researchers to investigate the use of solid surface catalysts as an environmentally-friendly alternative to toxic, costly, and non-reusable transition metal catalysts.[80] Alumina, silica, and zeolite catalysts are among the most popular oxide catalysts which are increasingly used as replacement technologies for metal catalysts.[81] Although many solid-phase catalysts share some general characteristics, i.e., high surface to volume ratio, only those reactions mediated by alumina or silica will be discussed here, with special emphasis on silica gel-mediated reactions.

Silica gel is manufactured by treatment of sodium metasilicate (Na_3SiO_3) with acid.[82] Typically, this involves sparging gaseous carbon dioxide (a weak acid) through a

dilute aqueous solution of sodium metasilicate until neutral pH is attained. At pH of 7, the mixture becomes gelatinous, and the sodium ions are washed away. High temperature baking (~200 °C) removes most of the excess water and leaves behind the amorphous silica gel. At higher temperatures, (> 500 °C) adjacent terminal siloxy groups condense, resulting in further dehydration and reduced acidity through loss of chemisorbed water molecules.

The catalytic cycle for heterogeneous reactions is somewhat more complex than its homogenous counterpart. Part of the complexity resides in the fact that the exact distribution of the catalyst in unknown. Additionally, the steps involved in mass transport of the reagents and products to and from the active site of the catalyst obscure the complete reaction picture. Augustine[82] has delineated some factors necessary for successful surface-catalyzed transformations: (1) the reagents must reach the active site; (2) they must interact with the catalyst; (3) the reaction proceeds to give products; (4) the products are desorbed from the catalyst; (5) the products (and unreacted starting materials) are transported away from the catalyst. Step five is an extremely important consideration. An aqueous work-up and final purification by silica gel chromatography are often necessary steps following homogeneous reactions. If one can carry out the same reactions on silica surface and simply desorb the reaction products by chromatographic elution following the reaction, several unnecessary operations are avoided and thus, time, materials, and mechanical losses are minimized in the process.

Several factors contribute to the enhanced reactivity of surface-mediated reactions. In contrast to homogenous reactions, in which all reactants are uniformly distributed throughout the reaction media, heterogeneous reactions depend on reactants

coming in contact at the surface of the active site. Silica gel has an extremely high surface to volume ratio; commercially available grade silica typically has a surface area of approximately 500 m^2/g. An important consideration for many processes is good thermal and mechanical stability over a wide temperature range; silica gel also displays these properties. Its compatibility with a broad range of solvents is attributed to the fact that silica gel does not swell in organic solvents. Aside from the rate enhancement due to its high surface area, silica gel possesses the unique property of having high silanol density. As depicted in Figure 8, the terminal silanol groups on the silica surface form a H-bond network, which dramatically enhances the rate of reactions requiring mild acid catalysis. This "network" of H-bonds postions the active catalytic residues in close proximity to the substrate, thereby lowering the transition state activation energy. The carbonyl group in Figure 9 is activated by H-bonding to a hydrogen atom on the terminal silanol functionality. This effect is magnified in silica gel which has been "activated" by dehydration. Silica gel can be readily activated by washing with polar solvents to remove residual water, followed by high temperature baking under reduced pressure, to remove excess solvent. Alternatively, commercially available silica gel may be "deactivated" by thorough mixing with 10% (w/w) water. Chromatographic separation of acid-sensitive compounds (epoxides, aldehydes, aziridines, etc.) often requires prior deactivation of silica gel.

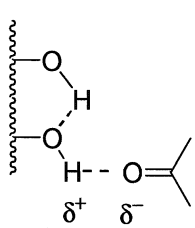


Figure 9. Activation of a carbonyl by H-bonding on the surface of silica gel.

II-2.1 Applications of Surface-mediated Catalysts

The first applications of surface-mediated reactions probably date back to the use of thoria (ThO_2) as a surface catalyst in the alkylations of aniline.[83] As an extention to that work, Brown and Reid employed silica gel as a Lewis acid catalyst in the alkylation of various amines with alcohol at high temperatures in 1924.[84] Silica gel also found early application in the production of formaldehyde.[85] Since these early reports, the solid state chemistry of alumina[76] and silica gel has been exploited in hydrolysis and deprotection reactions,[47] S_N2 reactions,[86] oxidations,[87] Diels-Alder cyclizations,[88] deoxygenation,[89] nucleophilic addition reactions,[90] and as a support for phase-transfer catalysts.[91] The reason for its broad application is primarily due to the combination of high surface area and the mildly acidic nature of alumina and silica. Silica gel, in particular, is a versatile catalyst, because of its ability to interact through both covalent and non-covalent interactions. The nature of the interaction of silica with certain co-ordinatively unsaturated metals is assumed to be a covalent association through its terminal siloxy groups.[92]

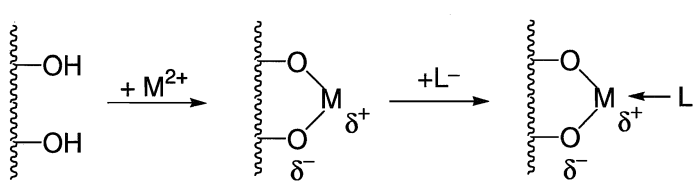
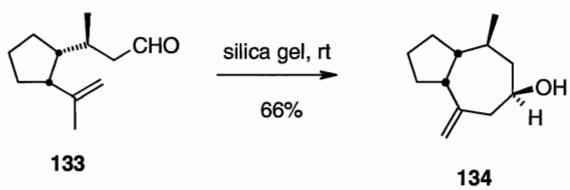


Figure 9. Convalent association of a metal to silica surface.

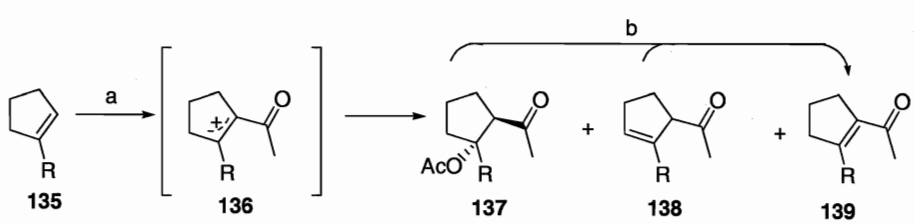
The utility of heterogeneous catalysis in liquid phase has been amply demonstrated by Hudlicky, who desribed the displacement reaction of alkylhalides with hydrozoic acid on

an alumina surface.[93] In this experiment, the reactants are simply applied to the top of an alumina column, and after 16 h reaction time, the desired azides were eluted with hexane and ether. In similar fashion, Marshall[94] synthesized hydroazulenes by chromatographic elution of aldehydes on silica gel, Scheme 6.



Scheme 6. Silica gel-mediated Prins-reaction.

The synthesis of acylated cycloalkenes catalyzed by alumina was reported in1981 by Hudlicky.[77a] The equilibrium mixture of acylated products was channeled to the desired α,β-unsaturated ketone **139** by adsorption of the crude mixture on alumina followed by elution with dichloromethane.

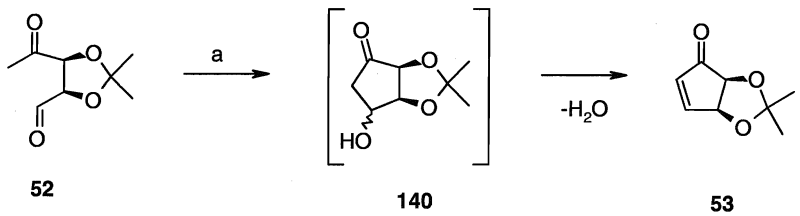


Reagents and Conditions: (a) Ac_2O, ZnI_2, $ZnCl_2$, 0 °C; (b) neutral alumina, rt (74%).

Scheme 7. Synthesis of α,β-unsaturated cyclic ketones.

As briefly mentioned in Section II-1.4, Hudlicky achieved a facile intramolecular cyclization of a keto-aldehyde in the formal synthesis of $PGE_{2\alpha}$ on the surface of

alumina.[13] The fact that other "standard" methods to effect this intramolecular condensation failed was noted by the authors.

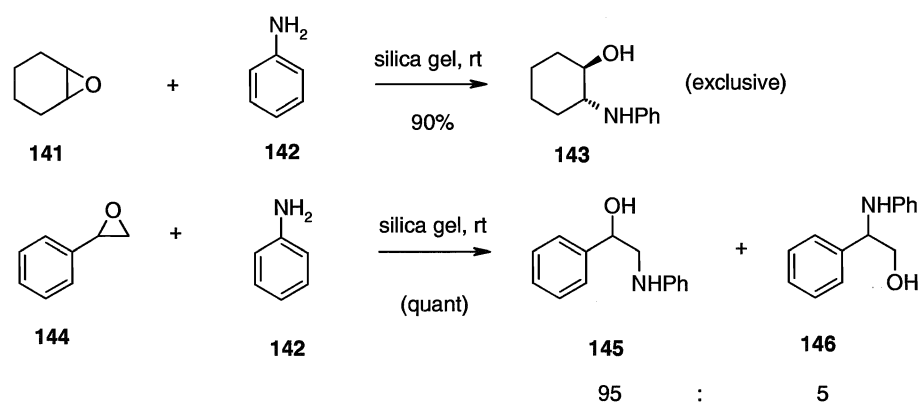


52 140 53

Reagents and conditions: (a) Alumina, DME, relflux (65%); (b) Alumina, benzene, reflux (65%)

Scheme 8. Synthesis of key intermediate in $PGE_{2\alpha}$ on alumina surface.

The opening of epoxides with amine nucleophiles represents a general entry into 1,2-*trans*-disposed amino alcohols, important intermediates in natural products[95] and asymmetric catalysis.[96] In an effort to access these materials in the abscense of protic or metal catalysts, Chakroborti[97] has recently reported a simple and mild catalytic system using silica at rt. The procedure simply calls for an addition of 1.0 equiv of the amine to a stirred suspension of 2.5 equiv of epoxide and silica gel (10% (w/w)) at rt. It is noteworthy that the authors report no reaction takes place in the abscence of silica gel.



141 142 143

144 142 145 146

95 : 5

Scheme 9. Silica gel mediated opening of epoxides.

As shown in Scheme 9, high selectivites for *trans*-disposed amino alcohols were obtained. Additionally, the catalyst could be re-used a number of cycles without loss in activity.

In 1996, Kotsuki and co-workers reports their results of a study directed at the opening of various benzylic epoxides with indole and pyrrole nucleophiles.[98] A comparison was made between nucleophilic openings facilitated by high pressure (10 kbar) and those reactions at rt under the influence of silica gel catalysis. Although the epoxide opening was significantly slower to react on silica, yields of the opened product were consistently higher. A plausible mechanism for the influence of silica gel was presented, see Figure 12.

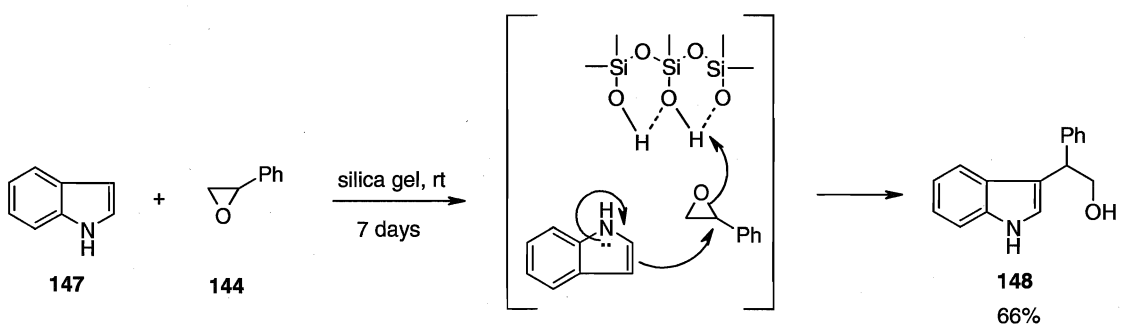
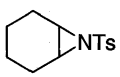
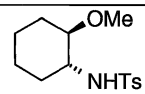
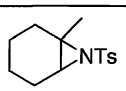
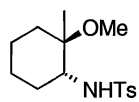
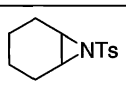
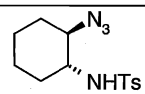
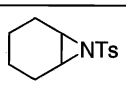
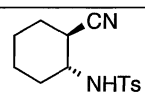
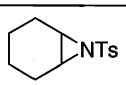
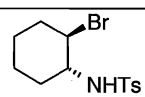
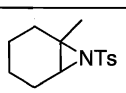
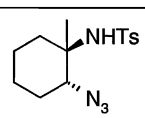


Figure 12. Mechanistic proposal for activation of epoxides by silica gel.

While aziridines are known to be more resistant to nucleophilic attack than their epoxide counterparts, they are readily opened by nucleophiles in high yield with phosphomolybdic acid supported on silica gel.[99] The use of activated surface catalysts in conjunction with PMA is a widely-used catalyst for vapor phase reactions; many of these systems have become commercially available.[100] Baskaran describes the opening of

various aziridines on silica surface treated with 1 mol% phosphomolybdic acid. The products shown below form exclusively under the conditions presented.

Table 2. Opening of Strained Heterocylcles on activated surface[a]

Substrate	Nucleophile	Product	Time (h)	Yield (%)[b]
	MeOH		0.5	91
	MeOH		0.25	95
	NaN_3		2.5	91
	NaCN		8	95
	KBr		10	95
	NaN_3		4	93

a 1 mol% PMA/SiO_2 in MeCN at rt
[b]Yields are isolated

There are several advantages associated with the use of silica gel as a mildly acidic catalyst. Aside from its low cost, silica gel is recyclable, readily available, and maintains its physical characteristics in a variety of solvents through a broad temperature range. Additionally, silica gel reactions often *require no solvent*, thereby reducing costly waste disposal. A last important consideration is that silica-gel mediated reactions are

generally operationally simple. With the growing number of expensive and specialty catalysts decribed in the recent literature, general protocols for facilitation of simple nucleophilic reactions are increasingly difficult to obtain. Chapter Three describes our development of such a general procedure using indole nucleophiles to open strained heterocycles and its eventual application in synthesis.

II-3 History of Morphine Synthesis

Morphine **149**, and its congeners codeine **17**, and thebaine **9**, have attracted the attention of chemists for nearly 200 years. The combination of their powerful biological activity and unique molecular architecture make the morphinan alkaloids both challenging synthetic targets and indispensable narcotics. Morphinan alkaloids isolated from the opium poppy, *Papaver somniferum*, have been used for thousands of years, although morphine was not isolated in its pure form until 1806 by Sertürner.[101] Several medicinally useful derivatives of this class of alkaloids, namely naltrexone **150** and naloxone **151**, are produced commercially and are frequently used to treat opiate overdoses and addictions. These derivatives, however, originate in synthetic manipulations of the parent alkaloids isolated from the opium poppy; to date no fully synthetic commercial route to morphine or its analogues exists.

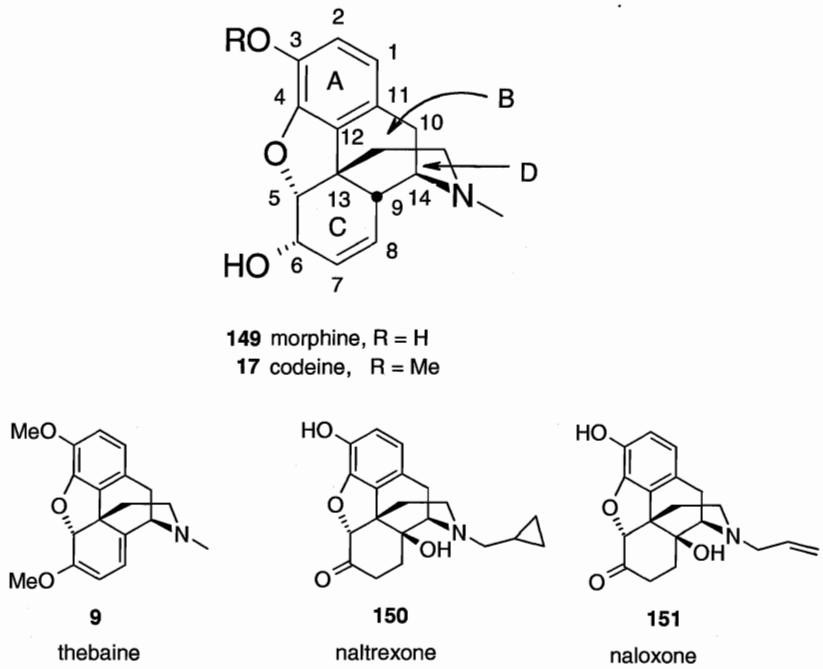


Figure 13. Morphine and its related derivatives.

Extraction of morphinan alkaloids from the opium poppy is a relatively simple process. The opium poppy seed pod is slit to allow excretion of the pinkish opium latex,[102] which is scraped from the surface and collected. The latex, which rapidly turns black on exposure to air, is allowed to bake in the sun to remove excess water. This crude product is termed *Indian opium*, and is comprised of more than 40 alkaloids, of which morphine is the chief constituent, representing approximately 10-15% of the mass. Morphine can be isolated in pure form according to the procedure reported by Sertürner.[103] The protocol involves trituration of Indian opium with hot water until the filtrates become colorless. The filtrates are then concentrated, diluted with water while still warm, and saturated with ammonia. The semi-crystalline material which precipitates is then diluted with water and triturated with ethanol.

Following Setürner's initial isolation of morphine, over 100 years of effort was devoted to its structural elucidation. Forty two years after the initial isolation of morphine, Laurent[104] disclosed its correct empirical formula-$C_{17}H_{19}NO_3$. The nature of the oxygenation was ascertained largely throught the work of Wright,[105] who is credited with the first synthesis of heroin, or, diacetylmorphine as a result of that work. Shortly after, in 1881, von Gerichten noted that distillation of morphine with Zn dust at 300 °C yielded phenanthrene.[106] Further degradive experiments of morphine and codeine by Hofman and Pshorr confirmed the prescence of an oxygenated phenanthrene skeleton.[107] Indeed, the work of Setürner, Pshorr, Knorr, Liebig, Laurent, and other pioneers of that time greatly accelerated development of the disipline of organic chemistry as a result of their pursuit of morphine structure elucidation .[108] It was not until 1926 that the correct connectivity of the pentacycle was proposed by Robinson,[109] and this proposal was ultimately proved correct by Gates in 1952,[111b] when the first synthesis of morphine was disclosed. Gates' completion of morphine is recognized as a landmark synthesis, not only for its confirmation of Robinson's proposed structure, but because it stands as an important illustration of the power of total synthesis as a tool in structure determination which stands to this day as the ultimate proof of structure.

Long after Gates' initial synthesis of morphine, it enjoys continued attention from the synthetic community. Despite the relatively small size of morphine (bearing only 17 carbons) it remains an extremely complex and dissonantly assembled[110] molecule. There are a number of unique structural features which contribute to its complexity as a synthetic target: the C-13 quaternary center, the C-4,C-5 ether linkage, five vicinal stereocenters, and the pentacyclic framework. Though not comprehensive, the

following section briefly describes a selection of synthetic efforts toward total synthesis of morphine alkaloids which employ Diels-Alder, radical cyclizations, or palladium cyclizations as key strategies.

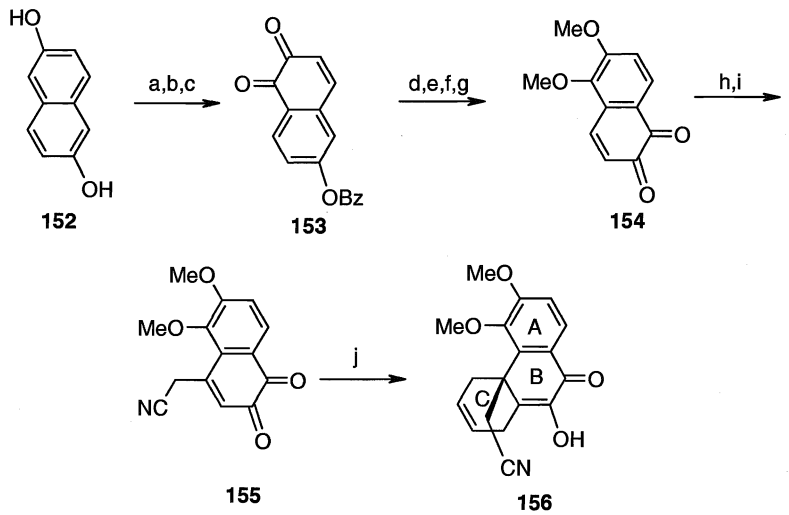
Though initially reported in 1928, the Diels-Alder reaction continues to find wide application in the synthesis of natural products. The broad applicability may be attributed to the stereospecific nature of the reaction and its ability to generate multiple ring systems (and therefore multiple stereocenters) in a single step. Several morphine approaches discussed in the following section have relied on the Diels-Alder reaction to forge the problematic C-13 quaternary center. Parker and Hudlicky have both considered radical-based approaches to the morphinan skeleton. Radical-initiated reactions are particularly attractive in that they are known to "zip up" the morphinan skeleton in single-operation cascade reactions, greatly shortening the length of the synthetic sequence. Finally, the utility of palladium catalysis will be highlighted as both a means to access to chiral synthons and as a powerful tool in the chemoselective generation of carbon-carbon bonds, the cornerstone of organic synthesis.

II-3.1 Approaches Toward the Synthesis of the Morphine Skeleton using Diels-Alder Cyclizations

Gates (1952, full disclosure in 1956)[111]

The first synthesis of morphine was completed in 1952 and spanned 24 steps in an overall yield of 0.02%. The synthesis began from 2,6-dihydronaphthalene **152**, a common material used in the synthesis of dyes. The symmetry in the starting material allowed Gates to carry out, in interative fashion, a nitrosation/ reduction/ oxidation

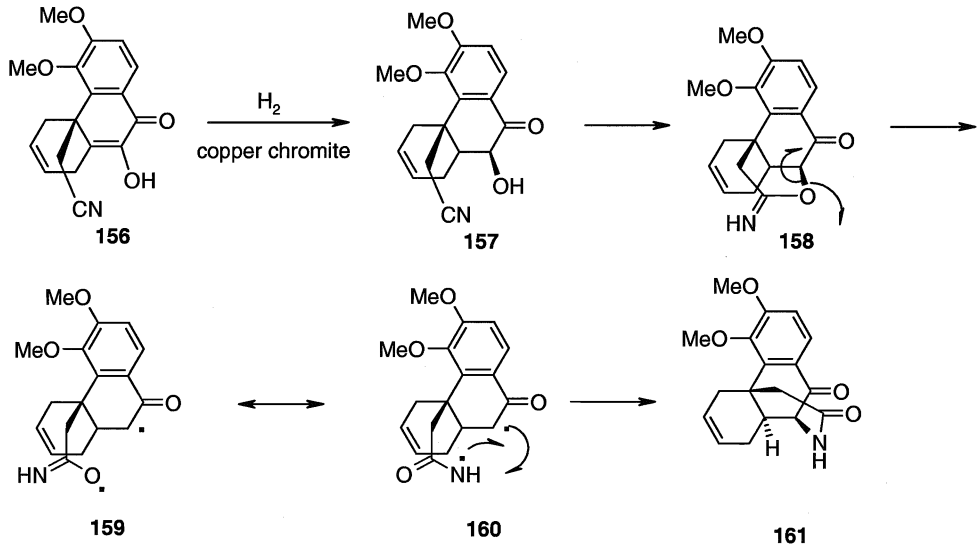
sequence on what was to become both the A- and B-rings to provide **154.** As was shown in earlier model studies,[112] the C-13 center could be forged using a Diels-Alder reaction of **155** with butadiene to give **156.**



Reagents and Conditions: a) BzCl, py, dioxane (72%); b) $NaNO_2$, AcOH (88%); c) AcOH, Pd(C), H_2, then $FeCl_3$ (85%); d) SO_2, MeOH, (91%); (e) K_2CO_3, dimethyl sulfite, f) KOH, MeOH, (87%); g) $NaNO_2$, AcOH, Pd(C), H_2, then $FeCl_3$, (82%), h) ethyl cyanoacetate NEt_3, then $K_3Fe(CN)_6$ (84%); i) Claisen's alkali, (97%); j) butadiene, (66%).

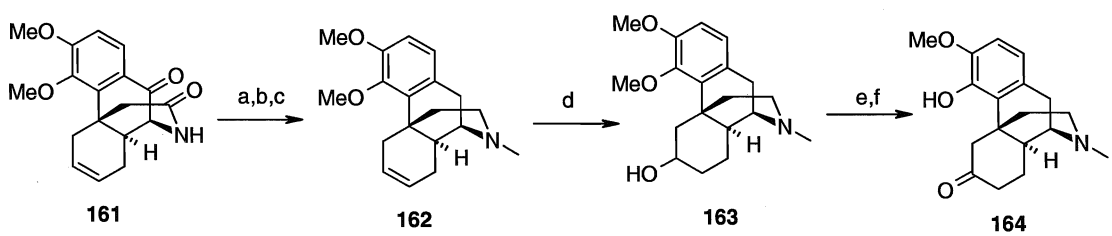
Scheme 9. Gates synthesis of morphine intermediate **156.**

The D-ring of morphine was installed in a rare reductive cyclization reaction mediated by copper chromite catalyst under a medium-pressure of hydrogen gas at 130 °C. The cyclization, discovered quite by accident in an earlier series of model studies, was published in 1950.[113] Gates, in his full disclosure of the synthesis of morphine,[111] stated that the course of this particular reaction "was far from clear". A mechanism for this fortuitous cyclization has been proposed and is shown in Scheme 10.[111]



Scheme 10. Proposed mechanism for the reductive cyclization.

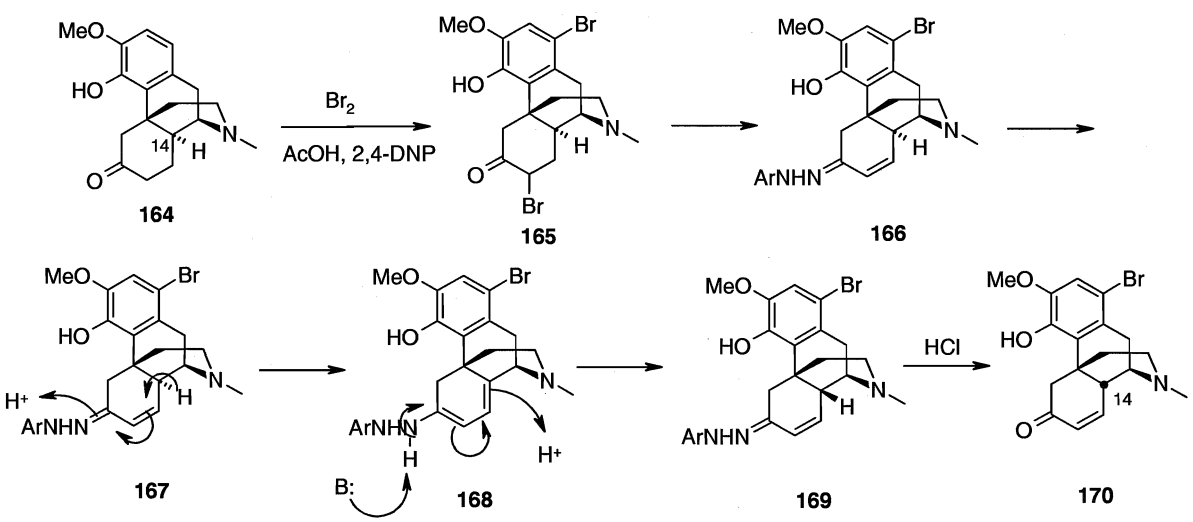
The product of reductive cyclization **161** was transformed to morphinan **162**, which represents the entire carbon skeleton of morphine, Scheme 11. Resolution of racemic **162** was accomplished by crystallization with the enantiomorphic dibenzoyltartrate salts. On a more practical note, having matched his synthetic *d*-*β*-Δ^6-dihydrodesoxycodeine methyl ethers with the natural material, Gates was now able to carry on the synthesis from natural derivatives. Oxidation at C-6 and selective demethylation gave the ketone **164**.



Reagents and Conditions: a) KOH, N_2H_2; b) NaH, MeI; c) LAH (54%); then dibenzoyl tartrate resolution; d) dilute H_2SO_4 (28%); e)KOH, ethylene glycol; f) *t*BuOK, Ph_2CO (89%);

Scheme 11.

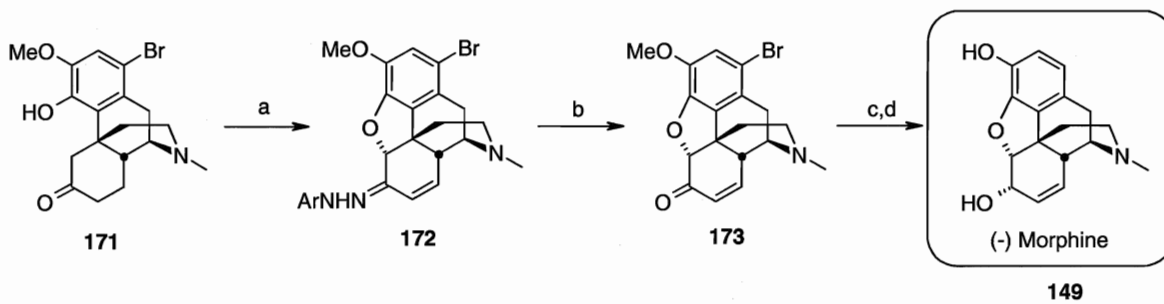
At this point, Gates faced the daunting task of establishing a cis-fused B and C ring system through inversion of the C-14 center. This problem was ultimately solved by treating the ketone **164** with 2 equivalents of bromine followed by hydrazone formation. Indeed, introduction of the α,β-unsaturation unit in compound **166** allowed the equilibration of the C-14 (morphine numbering) center, Scheme 12. Though an obvious equilibrium exists, the β-configuration of the C-14 hydrogen is energetically preferred. It is noteworthy that Gates' sequence remains, to this day, the method of choice for equilibration of the C-14 center in morphine alkaloids. A plausible mechanism for this valuable transformation is advanced in Scheme 12.



Scheme 12. Proposed sequence for C-14 epimerization via hydrazone formation.

The last significant challenge presented itself in the form of the C-4,C-5 dihydrobenzofuran closure. Once again, Gates turned to the very same set of conditions that so elegantly addressed the problem of C-14 epimerization.[114] To this end, ketone **95** was treated with bromine followed by 2,4-DNP, which-in a single reaction vessel-effected closure of the C-5 ether bond and introduced the $\Delta_{7\text{-}8}$ unsaturation unit.

Liberation of the ketone from its hydrazone precursor gave morphinan **173**, which was converted to morphine in two further steps.



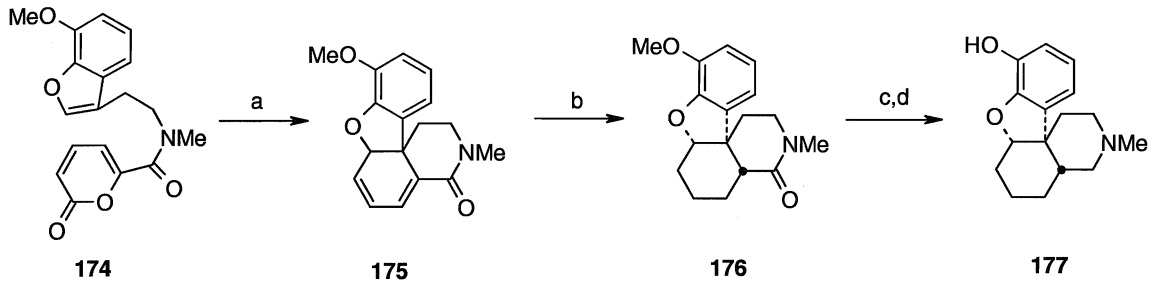
171 172 173 149

Reagents and Conditions: a) Br_2, AcOH, 2,4-dinitrophenylhydrazine (26%); b) 12N HCl in acetone (27%); c) LAH (quant); d) Py•HCl (34%).

Scheme 13. Gates final transformations to (-)-morphine.

Ciganek (1981)[115]

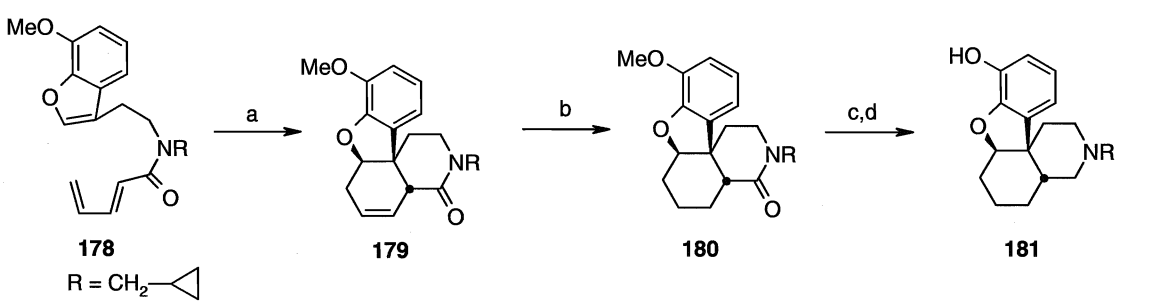
Partial syntheses of the morphinan skeleton continue to an important tool in the investigation of the structure activity relationship of morphine and its related compounds. In 1981, Ciganek disclosed one of the few approaches to a truncated morphinan skeleton which relies on a Diels-Alder reaction as the key transformation. The synthesis is unique in that it was the first reported application of a benzofuran unit as a Diels-Alder ene component and the approach utilized both tethered dienes and tethered pyrones as latent diene equivalents. The key step was the Diels-Alder cyclization of pyrone **174**, carried out in 1,2,4-trichlorobenzene at 215 °C to provide tetracycle **175** in 53% yield. The diene was then subjected to hydrogenation to yield the truncated morphinan **176**, bearing trans-stereochemistry at C-13 and C-9 (morphine numbering). Borane reduction of the amide and demethylation of the aryl ether provided compound **177**, whose structure was confirmed by X-ray crystallographic analysis of its methylcyclopropyl amine.



Reagents and Conditions: a) 215 °C; b) H_2, Pd/C; c) BH_3•DMS; d) nPrS$^-$K$^+$, DMF.

Scheme 14. Ciganek's synthesis of truncated morphinan derivatives.

Similar fused ring systems were obtained in the diastereomeric series from the tethered diene, albeit in significantly lower yields (10%). Diene tethered amide **178** was heated at 240 °C in toluene, affording the cis-fused morphinan **179** in 10% yield. Repetition of the hydrogenation and amide reduction gave **181**, which proved to be the diastereoisomer of derivative **177** previously synthesized from the pyrone cycloaddition. The relative configuration of this morphinan was assigned by analysis of a single–crystal X-ray structure. An alternative benzofuran Diels-Alder approach to morphine has been pursued by Stork and was recently completed.[116]

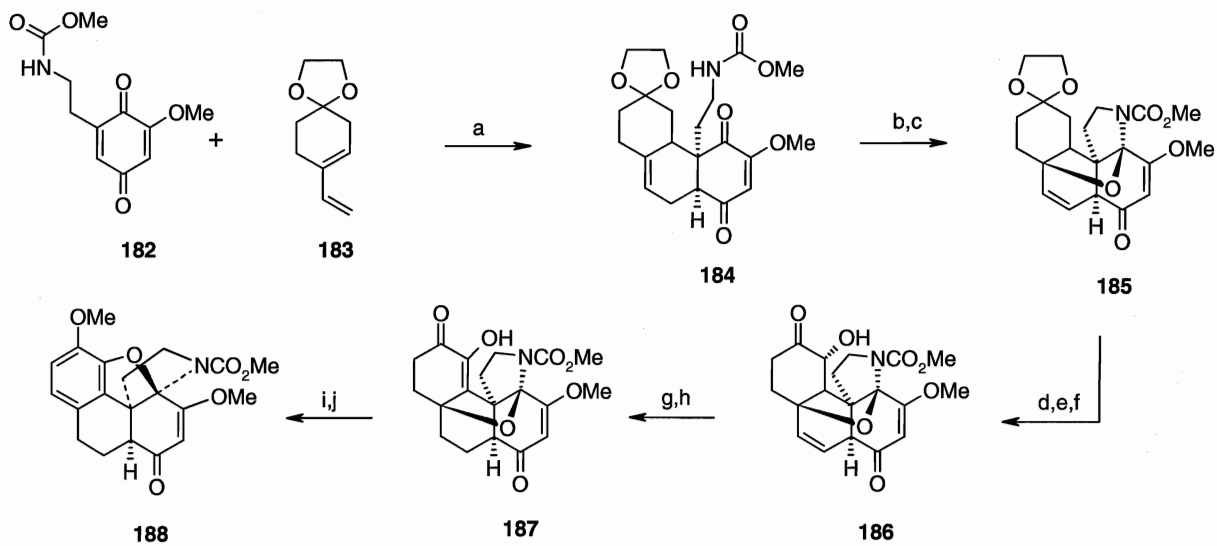


Reagents and Conditions: a) 240 °C; b) H_2, Pd/C; c) BH_3•DMS; d) nPrS$^-$K$^+$, DMF.

Scheme 15. Ciganek's synthesis of morphinans from diene-tethered benzofurans.

Tius (1992)[117]

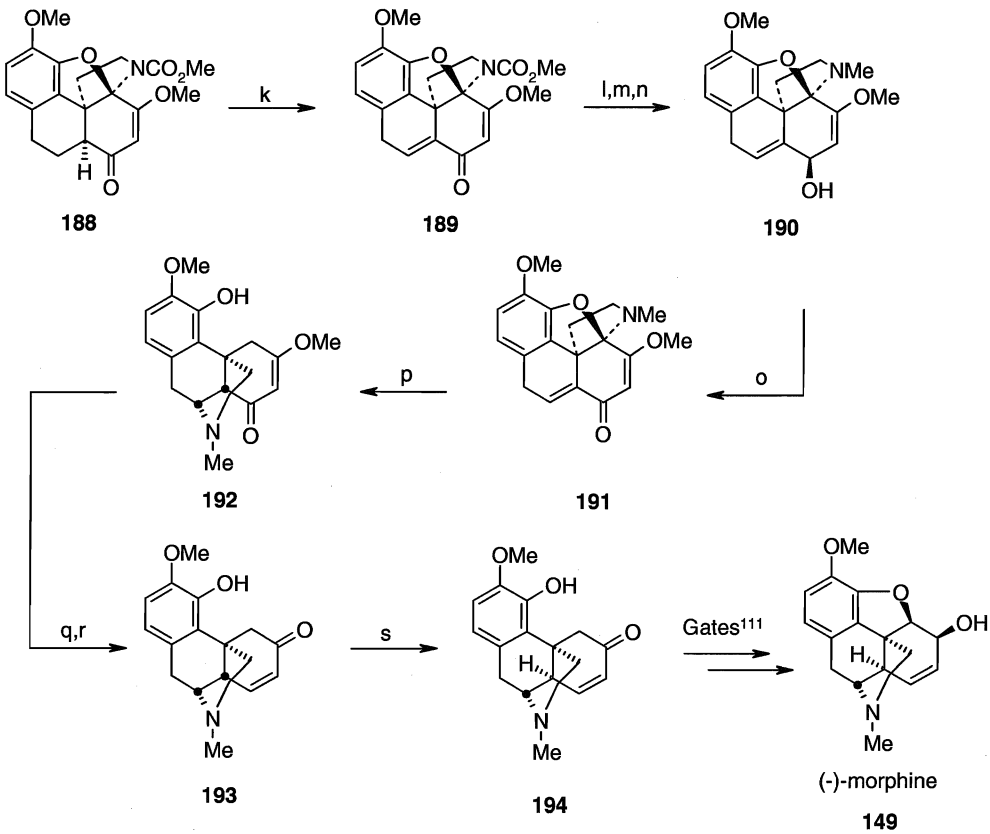
Tius reported an interesting approach which involved a Diels-Alder reaction of a suitably functionalized quinone with a styrene equivalent. Remarkably, the approach constitutes the only route originating in a non-aromatic A-ring. Their strategy is unique in that it offers, in a single operation, construction of the A, B, and C-fused ring systems common to the morphine alkaloid family. The difficult issue of C-13 center formation is thus addressed early in the synthesis through a quinone Diels-Alder reaction. The substituted quinone **182**, prepared in 7 steps from commercially available *o*-vanillin, was reacted with masked styrene **183** to provide the *endo*-Diels-Alder adduct **184** as a single isomer. The stereochemistry of **184** was rigorously established by single crystal X-ray diffraction. While attempting to install a functional handle for oxidation of the A-ring through chloroselenation, an unusual tandem selenocyclization was uncovered which led to oxo-bridged adduct **185**. The ketone was liberated and subjected to Davis oxidation, followed by hydrogenation of the 10-11 bond over Pd/C. A Swern oxidation of this material led to a re-aromatized derivative, which was converted directly to its methyl ether **188** upon re-aromatization.



Reagents and Conditions: a) toluene, 100 °C (86%); b) PhSeCl, MeOH; c) H_2O_2, THF (80%); d) aq HCl, THF; e) KHMDS, THF; f) 3-phenyloxaziridine, THF (82%); g) H_2, Pd/C, THF (75%); h) TFAA, DMSO, NEt_3; i) BF_3•Et_2O; j) CH_3I, K_2CO_3 (56% over three steps).

Scheme 16.

Several unsuccessful attempts were made to reductively cleave the N-C bond with retention of the dihydrofuran ring. The problem was ultimately solved by cleavage of both the C-N and dihydrofuran rings, and adjusting the oxidation state of the C-ring to allow re-attachment of the aminoethyl bridge, Scheme 17. To this end, **188** was treated with PhSeCl followed by oxidative work-up to give **189**. The N-methyl functionality was installed in three steps affording **190**. The allylic alcohol was then re-oxidized with the Dess-Martin reagent. Reduction of the dihydrofuran and pyrrolidine ring promoted a conjugate addition of the amine onto the α,β-unsaturated ketone to give the morphinan **193**. The final transformations to thebainone-A involved a [1,3]- transposition of the ketone and acid-catalyzed epimerization of the C-14 hydrogen. Gates had previously converted thebainone-A and β- thebainone-A to morphine,[111] and thus, Tius and Kerr achieved a formal synthesis of morphine in 24 steps.



Reagents and Conditions: k) PhSeCl, EtOAc, then H_2O_2, THF (70%); l) $NaBH_4$, MeOH; m) MeLi, THF; n) HCOH, $NaCNBH_3$, H_2O, CH_3CN (54% over three steps); o) Dess-Martin periodinane, CH_2Cl_2 (75%); p) Zn, NH_4Cl, EtOH, H_2O (73%, 60% conversion); q) DIBAL-H, THF; r) H_3O^+ (quant); s) HOAc, 100 °C (87%).

Scheme 17. Tius's final transformations to thebainone-A.

Hudlicky (1995)[118]

The Diels-Alder reaction has been exploited in the synthesis of a great number of natural products and derivatives. Here, Hudlicky has applied the Intramolecular Diels-Alder reaction of Furan (IMDAF) reaction toward the synthesis of the isoquinoline derivatives, a structural motif common to all morphine alkaloids.

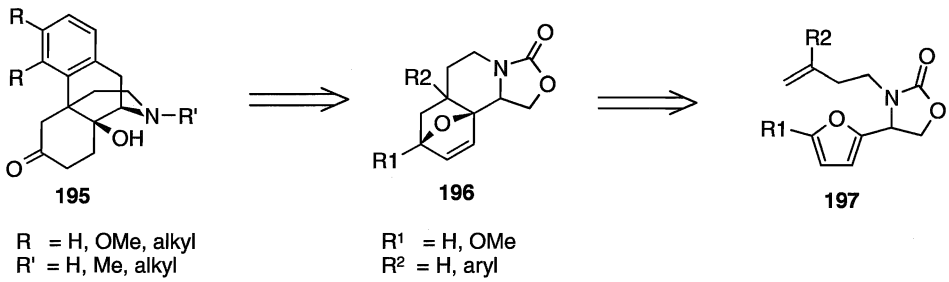
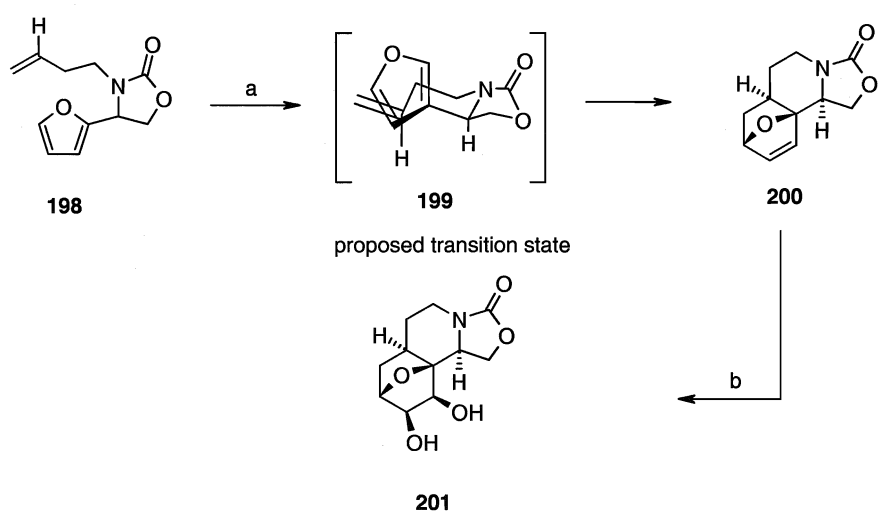


Figure 14. Retrosynthetic analysis of Hudlicky's approach to isoquinoline morphine synthons.

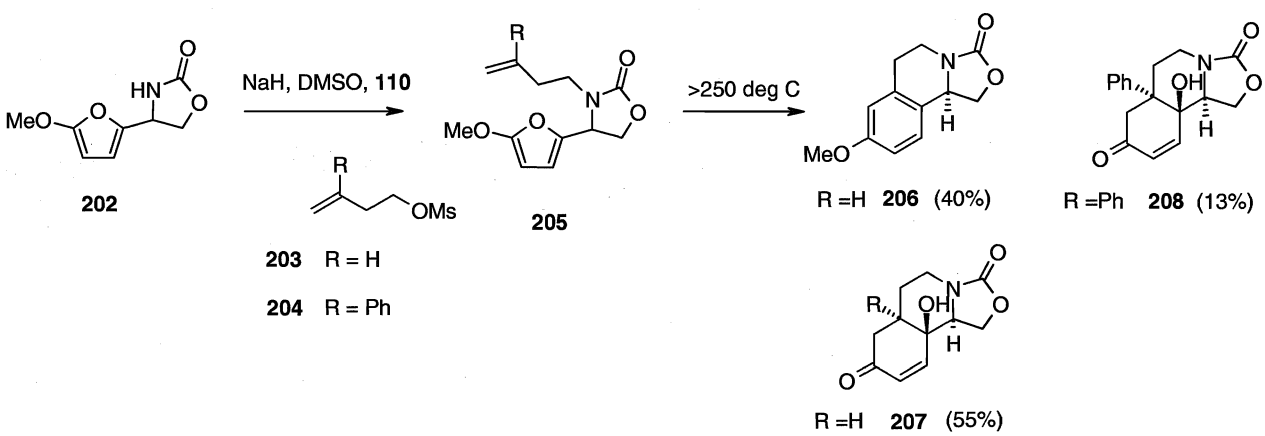
Model tricyclic systems were synthesized from olefin-tethered oxazolidinone **198**, which underwent thermal Diels-Alder cyclizations either by simple heating in toluene at 200 °C (56%), or facilitated at much lower temperature (65-90 °C) by the addition of β-cyclodextrin (84%). The stereochemistry of the model tricycle was rigorously proven by single-crystal X-ray analysis of the cis-diol **201**. Based on this evidence, Hudlicky postulated that the transition state favors a chair-like conformation in which the furan adopts an exo-position as shown in Scheme 18.



Reagents and Conditions: a) 90 °C, cyclodextrin (84%); b) OsO_4, *t*BuOH-H_2O (95%).

Scheme 18. Proposed transition state postulated for model isoquinoline cyclizations.

While the somewhat more sensitive 2-methoxyfuran fuctionality proved unstable toward β-cyclodextrin catalysis, 2-methoxy-furanyl systems were found to readily undergo thermal cyclizations at 165 °C to give the anisole **206** (40%) and the enone **208** (55%) on simple, mono-substituted olefins. It is noteworthy that the oxo-bridged adduct was neither isolated nor detected in crude reaction mixtures. The most advanced model addressed the problem of installing the quaternary center via a Diels-Alder reaction. According to this strategy, 2-methoxyfuran oxazolidinone **202** was alkylated with mesylate **204** and the resulting compound heated in toluene in a sealed tube to provide 13% of advanced isoquinoline derivative **207**. The stereochemistry of this compound was established by correlation with analogous Diels-Alder adducts.



Scheme 19.

Hudlicky (1992, 1998)[62]

The aromatic dioxygenases discovered by Gibson are unique in that both the chiral cyclohexadiene-cis-diol and its corresponding catechol are available from enzymatic transformation of parent aromatic compounds. A close inspection of the morphinan skeleton reveals that the A and C rings may be dissected into elements of both the cyclohexadiene-cis-diol and the catechol functionality. Hudlicky envisaged a pseudo-

symmetric approach to morphine in which both "halves" of the molecule may be accessed through bio-transformation of aromatic compounds. Tethering the two pieces at C-5 (morphine numbering) would set the stage for a Diels-Alder reaction to form the dihydrobenzofuran core of the natural product.

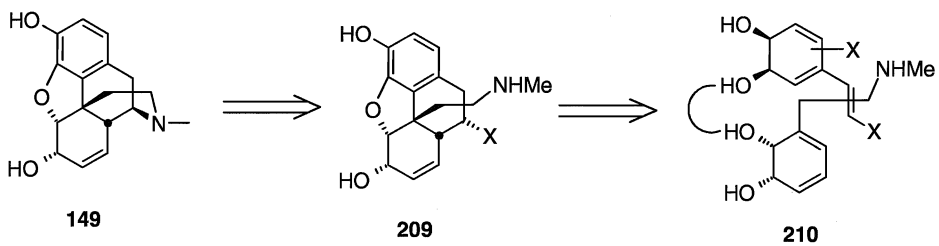
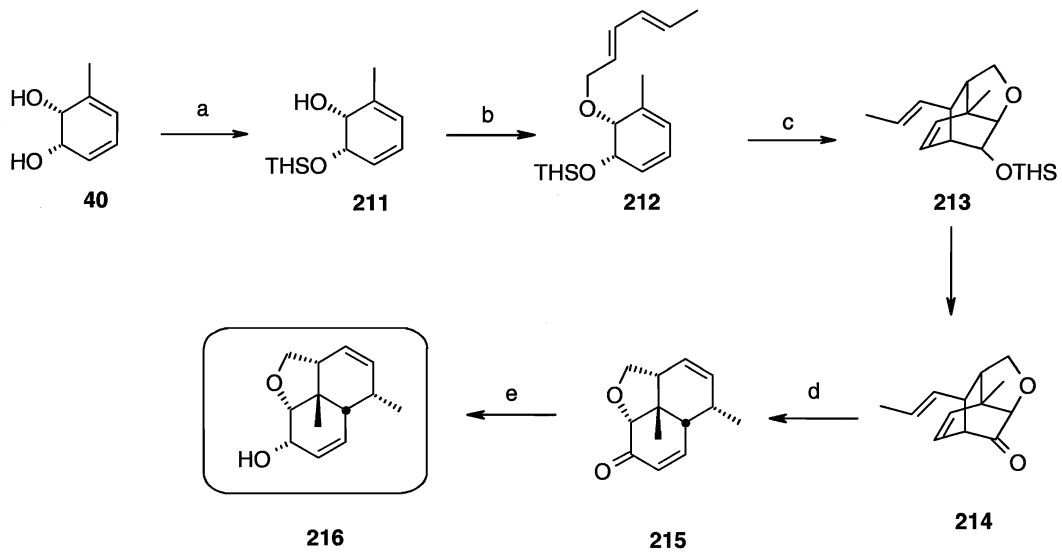


Figure 15. Hudlicky's retrosynthetic analysis of morphine through a Diels-Alder reaction.

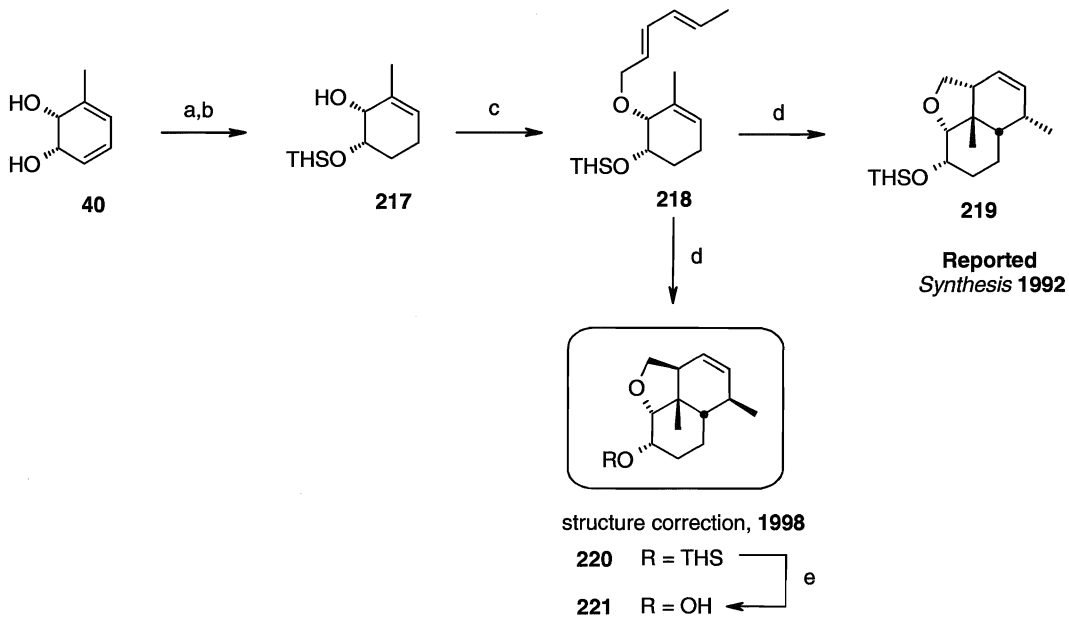
A preliminary model study, published in 1992, disclosed the synthesis of truncated morphine derivatives **215** and **216**. Dienediol **40**, available from whole-cell fermentation of toluene with *E. coli* JM109 (pDTG601), served as starting material for the model study. The tetraene **212,** rapidly assembled from toluene dienediol, was heated to give the Diels-Alder adduct **213** as shown in Scheme 20. The expected Cope rearrangement to tricycle **213** could only be effected after deprotection and oxidation of the alcohol to its ketone. Luche reduction of the α,β-unsaturated ketone gave allylic alcohol **216** possessing four stereocenters of the morphine skeleton in the correct configuration.



Reagents and Conditions: a) THS-Cl, imid; b) NaH, sorbyl bromide; c) CCl_4, reflux; d) TBAF, then PCC, rt; e) xylenes, 250 °C; $CeCl_3$, $NaBH_4$.

Scheme 20. Hudlicky's synthesis of truncated morphine derivatives.

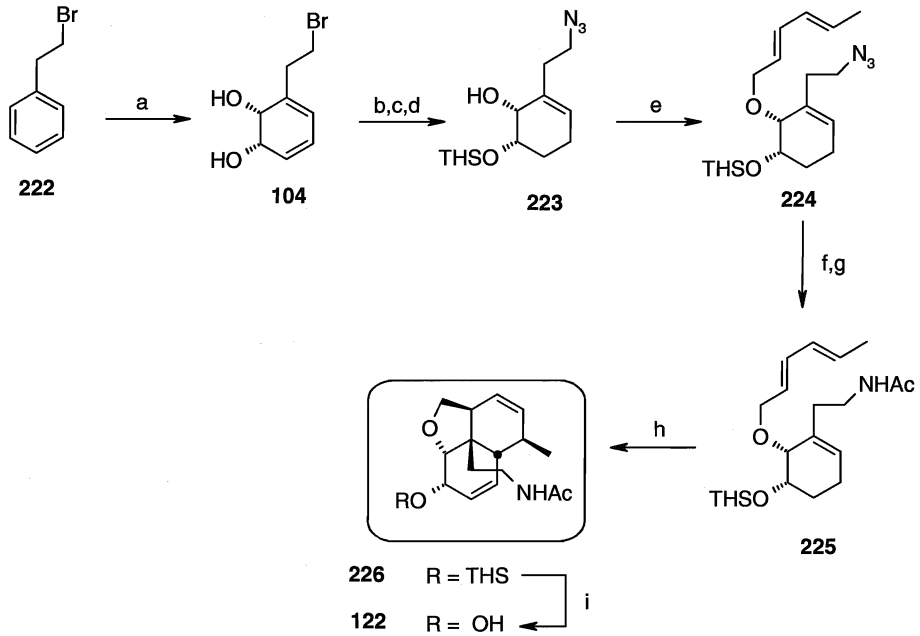
A similar model study was carried out using triene **218**, which provided adduct **220**, Scheme 20. Intramolecular Diels-Alder cyclization of **218** proceeded to give a single diastereomer, whose structure was originally mis-assigned as **219** based on nOe correlations in the NMR spectrum.



Reagents and Conditions: a) PAD, AcOH, MeOH; b) THS-Cl, imid; c) NaH, sorbyl bromide; d) toluene, 210 °C; e) TBAF, THF.

Scheme 21. Hudlicky's correction of structure for truncated derivatives.

The error was detected when a more sophisticated model system was later developed bearing the requisite nitrogen functionality for closure of the D ring. A single crystal X-ray structure analysis of the free alcohol **122** revealed that the [4+2] cyclization had proceeded through an *exo*-transition state, not through the *endo*-transition state as originally expected. At this point, the cyclization of **218** was repeated, and the silyl group removed following cyclization. A single crystal X-ray analysis of the resulting alcohol **221** established that, analogous to amide **225**, the cyclization proceeded through an unexpected *exo*-transition state. The synthesis of **122** is of some import, as it provides a very direct route to truncated morphinans possessing all of the stereocenters of the natural product in correct configuration.



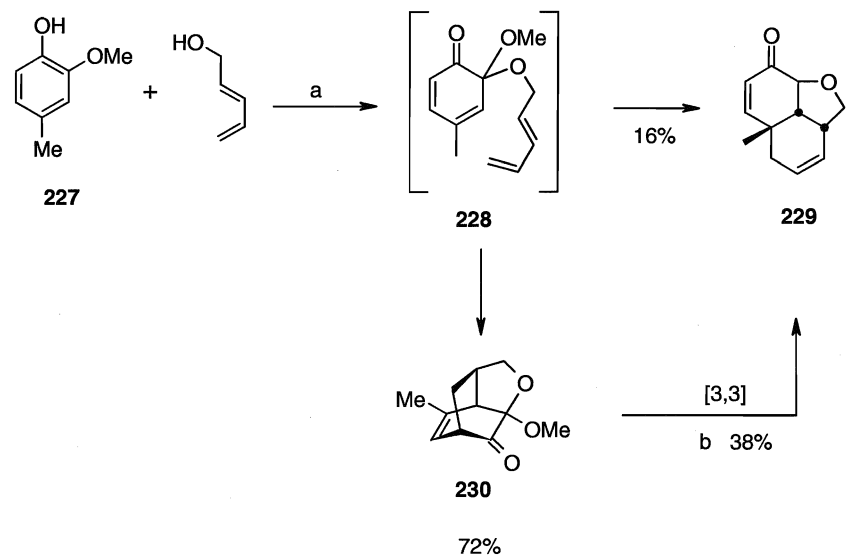
Reagents and Conditions: a) *Escherichia coli* JM109 (pDTG601); (10 g/L); b) NaN_3, DMF; c) PAD, AcOH, MeOH (72%); d) THS-Cl, imid, DMF (99%); e) NaH, sorbyl bromide, THF (62%); f) Ph_3P, H_2O (66%); g) Ac_2O, py (quant); h) toluene, sealed tube, 230 °C (62%); i) 45% aq HF, MeCN (65%).

Scheme 22. Hudlicky's approach to the B,C,D ring system of morphine.

Rodrigo (1998)[119]

A stragetically similar Diels-Alder approach to that of Hudlicky was described by Rodrigo. The approach exploits the tendency of *o*-substituted phenolic ethers to undergo oxidative coupling with alcohols to give mixed ketals. In this manner, ketal formation effectively tethers the diene to the ene, facilitating an intramolecular Diels-Alder reaction as depicted in Scheme 23. The elegance in Rodrigo's strategy is that regardless of which of the two possible Diels-Alder reactions take place, the products are degenerate. That is, the cycloaddition product arising from an "aromatic" diene gives a bridged bicycle **230**,

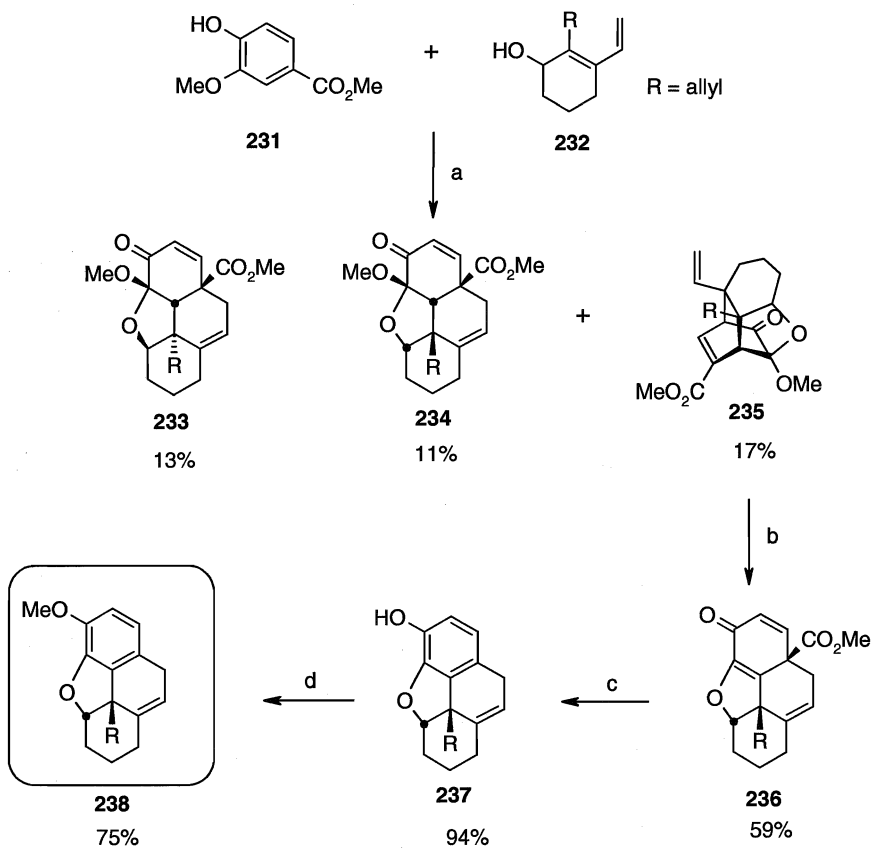
which rearranges to give the regio-isomeric Diels-Alder product **229**.



Reagents and Conditions: a) BTIB, THF; b) [3,3]-sigmatropic rearrangement

Scheme 23.

Rodrigo then embarked on a more advanced model employing methyl vanillate **231** as the ortho-quinone ketal precursor and allyl-substituted allylic alcohol **232** as the diene component. In this way, the reaction sequence can be extended to give the phenanthrofuran skeleton, comprising the A,B, and C rings of the morphine skeleton. Treatment of these precursors with BTIB resulted in the formation of three Diels-Alder adducts. Diastereomers **233** (13%) and **234** (11%) result from Diels-Alder addition across the diene, whereas the bridged bicycle **235** (17%) is derived from [4+2] cyclization with the diene component derived from the quinone. Thermal Cope rearrangement of this compound gives the tetracycle **236**, which undergoes rearomatization to **237** upon saponification of the ester. Finally, the phenol was alkylated using potassium carbonate and dimethyl sulfate to give the phenanthrofuran skeleton **238**.



Reagents and Conditions: a) BTIB, THF; b) DME, reflux; c) NaOH, MeOH; d) K_2CO_3, Me_2SO_4.

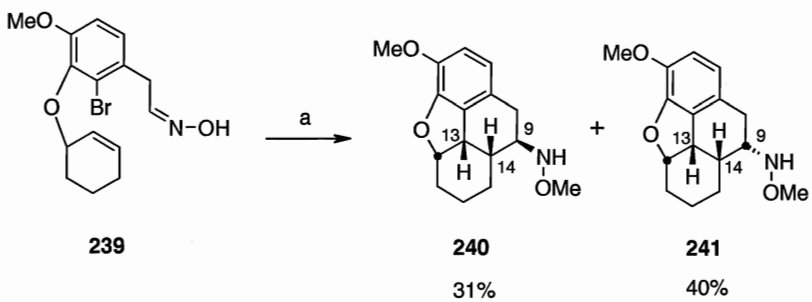
Scheme 24. Rodrigo's *o*-quinone Diels-Alder/Cope approach to phenanthrofurans.

II-3.2 Approaches to Mophine Involving Radical Cyclizations

Parker (1992, 1994)[120, 121]

Radical-cascades are remarkable in their ability to assemble complex ring systems in a single operation. Their application in the synthesis of morphine, therefore, promises to greatly shorten the overall synthetic sequence and address difficult tactical issues, such as C-13 bond formation. Parker's original approach is based on a tandem radical cyclization of an ortho-allyloxyl radical.[122] As an extention to this original work, Parker

reported the radical cascade of *o*-methyloxime **239** as a rapid entry to the morphine skeleton, Scheme 25.



239 **240** 31% **241** 40%

Reagents and Conditions: a) nBu$_3$SnH, AIBN, toluene, 110 °C.

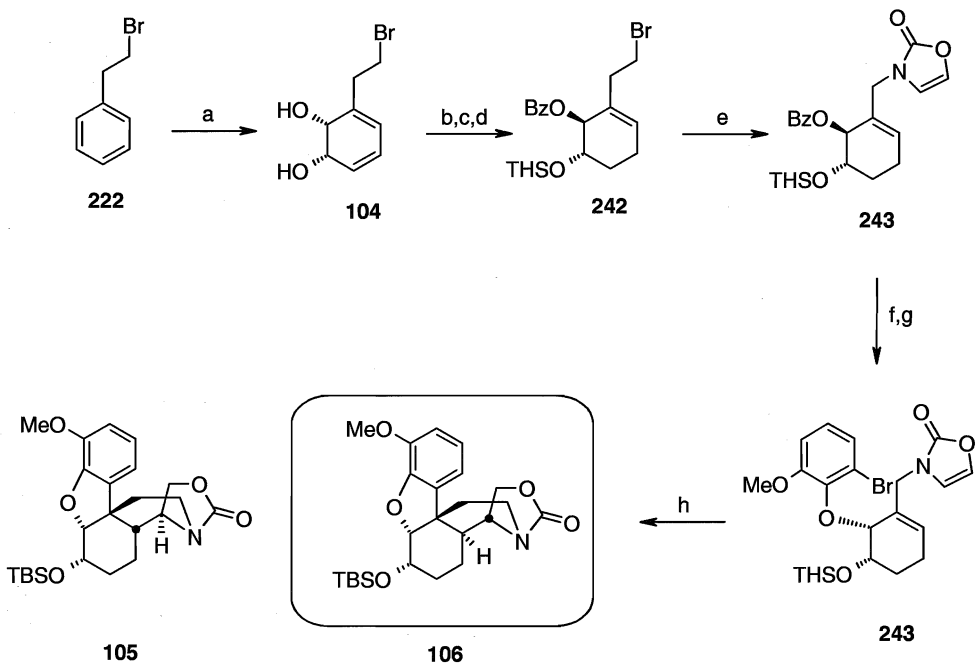
Scheme 25. Parker's first generation cascade approach to morphine.

Thus, in a single operation, the radical cascade provided morphinan derivatives **240** and **241**, in which the correct relative stereochemistry at C-5, C-13, and C-14 was established. The approach, however, failed to impart high selectivity in the relative stereochemistry at C-9, giving only 31% of the "natural" isomer **240**. An alternative approach in the racemic series addressed this issue and substitution at C-13. These model studies culminated in a total synthesis of racemic dihydroisocodeine in 11 steps from commercially available *m*-methoxyphenethylamine. The synthesis was later re-designed in the chiral sense- a summary of this work appears in a later section of this chapter.

Hudlicky (1996, 1998)[123]

Hudlicky's radical cascade approach resembled Parker's in that the initial radical would originate in the aromatic A-ring, which would be introduced through Mitsunobu alkylation of an appropriately substituted C-ring. In this case, the C-ring was fashioned from diol **104,** obtained from whole-cell fermentation of bromoethylbenzene with *E. coli* JM 109 (pDTG601). A key issue here was the inversion of C-5 through an initial

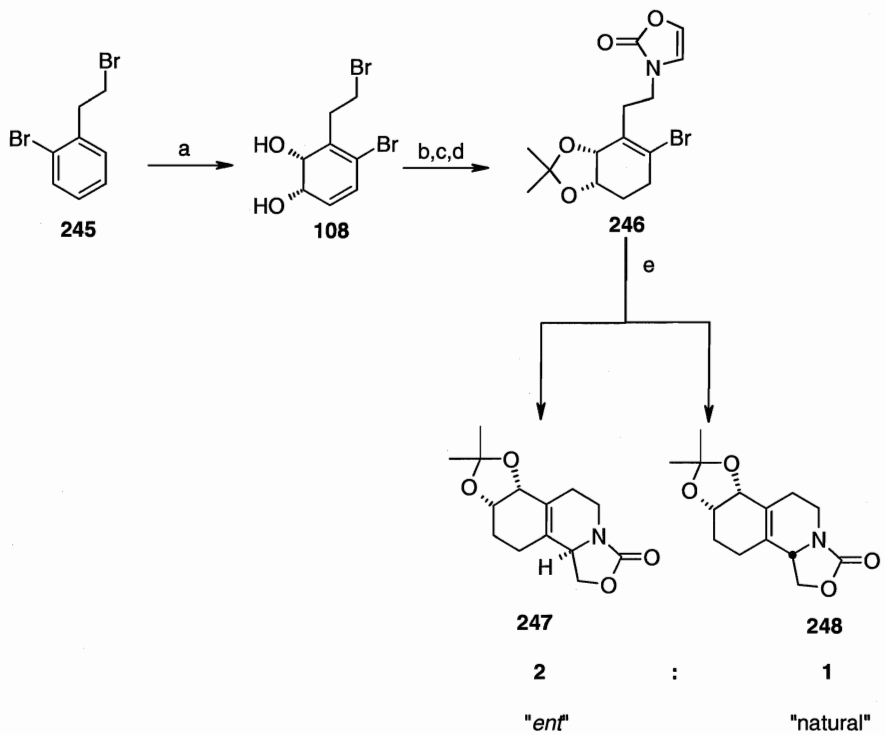
Mitsunobu reaction, and introduction of the aromatic piece through a second Mitsunobu operation. Initiation of the radical cascade gave a predominatly one diastereoisomer, morphinan **106,** albeit in a low yield. The presence of diastereomer **105** was also detected, however, this isomer was not rigorously characterized.



Reagents and Conditions: a) *Escherichia coli* JM109 (pDTG601); b) Potassium azodicarboxylate (PAD), AcOH, MeOH 80%); c) TBS-OTf, *i*PrNEt$_2$, CH_2Cl_2 (47%); d) PhCOOH, Bu_3P, DEAD (84%); e) NaH, 2-oxazolidinone, DMSO (71%); f) NaOH; g) 2-bromoisovanillan, Bu_3P, DEAD (28% over two steps); h) $(TMS)_3SiH$, AIBN, PhH (15%).

Scheme 26. Hudlicky's first generation radical approach to morphine.

The lack of stereoselectivity in the first generation approach prompted the design of a stepwise radical closure which would improve the yield of the isomer having the correct stereochemistry at C-13, C-14, and C-9. The approach relied on an initial radical-based closure of bromide **246** to give an advanced isoquinoline synthon **248**, Scheme 16.

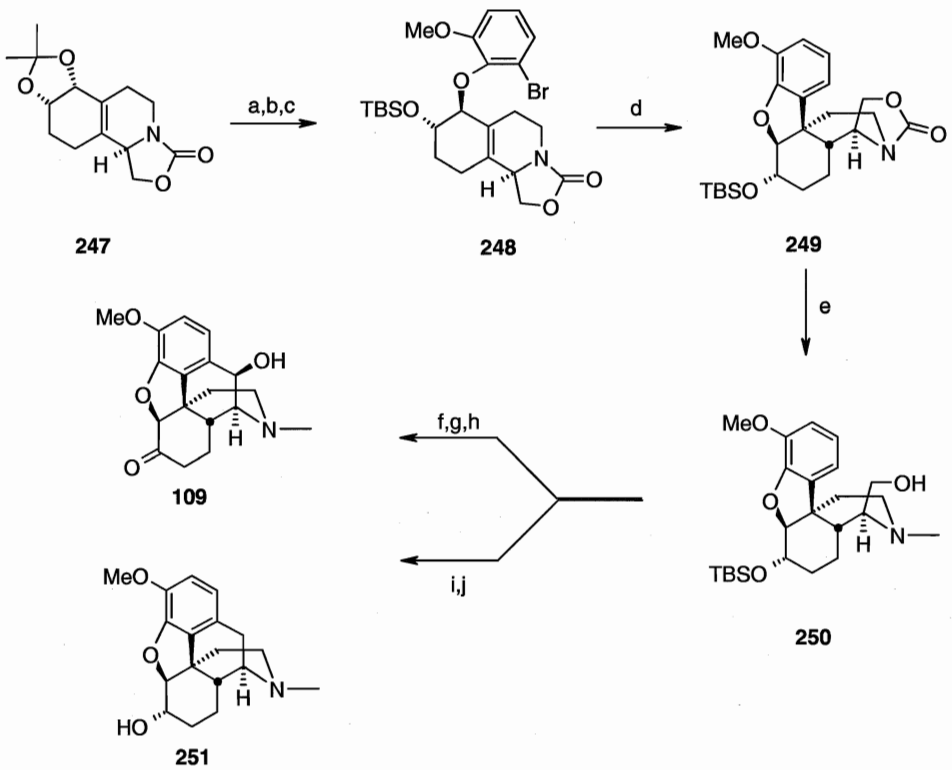


Reagents and Conditions: a) *Escherichia coli* JM109 (pDTG601); b PAD), AcOH, MeOH (50%); c) 2,2-dimethoxypropane, *p*TsOH (90%); d) NaH, 2-oxazolidinone, DMSO (38%); e) nBu$_3$SnH, AIBN (87%).

Scheme 18. Hudlicky's second generation "stepwise" radical approach to morphine.

Exposure of bromide **246** to tributyltin hydride/AIBN gave a 2:1 ratio of diastereomeric isoquinolines in 87% yield. The predominant isomer, which displayed an α-hydrogen, was to become *ent*-configuration C-9 (morphine numbering) center and the synthesis of unnatural (+)-morphine was pursued with this in mind. Introduction of the aromatic A-ring by Mitsunobu alkylation furnished the radical cyclization precursor **248**. Indeed, exposure of **248** to tributyltinhydride and AIBN gave a single diastereoisomer **249** in 47% yield. Unmaksing the oxazolidinone with DIBAL installed the N-methyl functionality and primary alcohol at C-10. The alcohol was initially oxidized to its aldehyde and treated with trifluoromethane sulfonic acid to induce Friedel-Crafts closure

of the C-10-C-11 bond. Alternatively, the *des*-oxy C-10-C-11 bond formation was achieved by conversion of the alcohol to its chloride and treatment with aluminum chloride.



Reagents and Conditions: (a) Dowex 50X8-100, MeOH (94%); (b) TBS-OTf, *i*PrNEt$_2$, CH_2Cl_2 (85%); (c) 2-bromoisovanillan, Bu_3P, DEAD (94%); (d) Bu_3SnH, AIBN (47%); (e) DIBAL, CH_2Cl_2 (87%); (f) TBAF, THF (quant); (g) $(COCl)_2$, DMSO (66%); (h) CF_3SO_3H (58%); (i) MsCl, Et_3N, LiCl (87%); (j) $AlCl_3$, benzene.

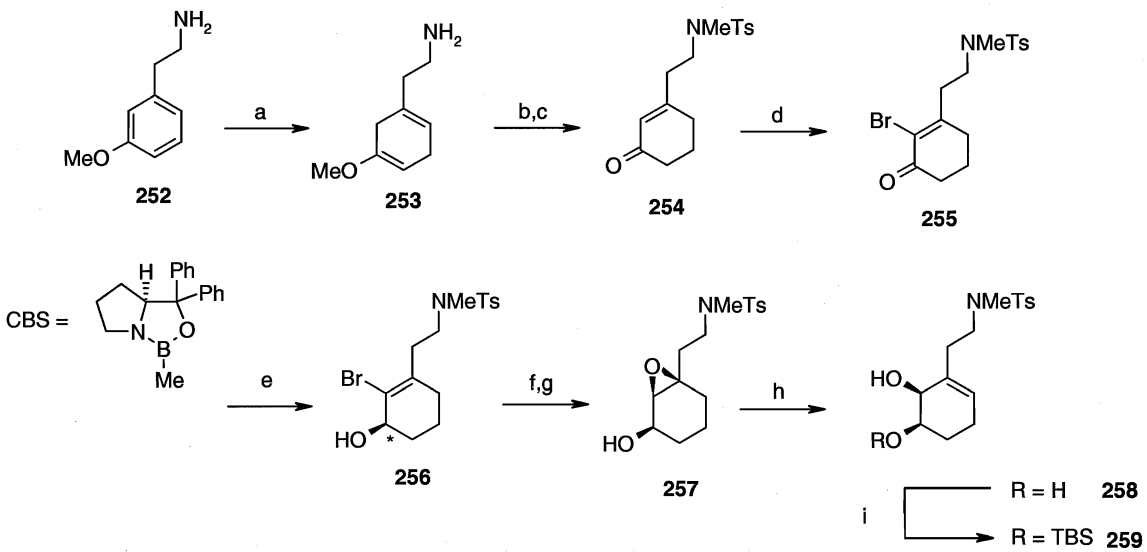
Scheme 28. Hudlicky's second generation radical approach toward *ent*-morphinans.

Parker (2006)[124]

Parker's original synthesis of racemic dihydrocodeine, in which the morphine skeleton was rapidly constructed through a radical cascade, was revisited in the chiral sense, leading to an asymmetric synthesis of (-)-dihydrocodeinone. The key features of the synthesis include elaboration of the asymmetric C-ring through Birch reduction, acidic hydrolysis, and chiral reduction of the corresponding enone, and a radical-based

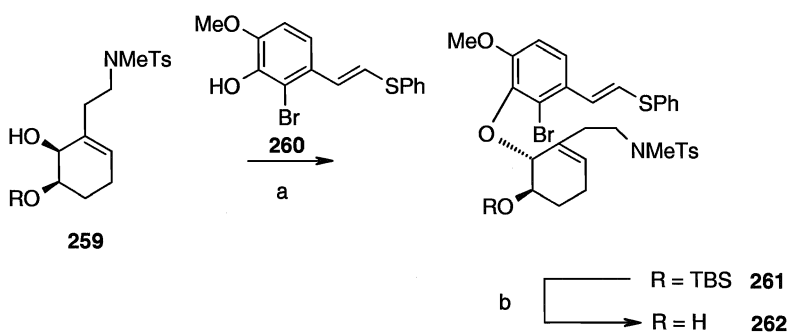
cascade which set the C-5, C-13, and C-14 centers of the natural product. The final step, a reductive de-tosylation, fortuitously installed the ethylamine bridge with correct stereochemistry at C-9.

It is noteworthy that the diol **258** is very nearly the enantiomer of the arenediol derived from fermentation of azidoethylbenzene, a synthon which will find application in the several morphine approaches decribed in Chapter III-6.4.



Reagents and Conditions: a) Li, NH_3, *t*-BuOH (97%); b) TsCl, NEt_3, then HCl (81%); c) MeI, K_2CO_3, acetone (96%); d) Br_2, NEt_3 (91%); e) CBS reagent, catechol borane (84%); f) Na, Hg (90%); g) *m*CPBA (92%); h) $Ti(OiPr)_4$ (85%); i) TBS-Cl, imid., DMF.

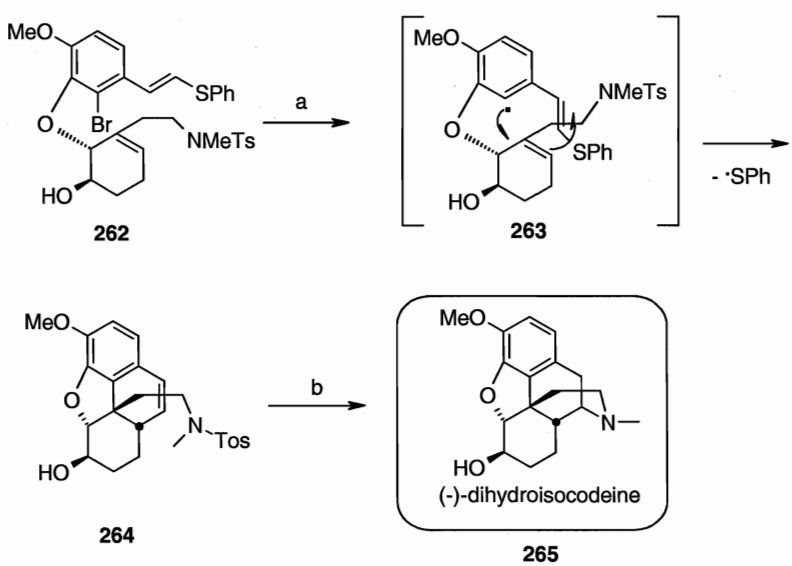
Scheme 29. Parker's asymmetric synthesis of the C-ring of morphine.



Reagents and Conditions: a) PBu_3, DEAD (83%); b) 10% HF, CH_3CN (78%).

Scheme 30. Introduction of the A-ring by Mitsunobu alkylation.

The aromatic A-ring was introduced via a Mitsunobu reaction[125] with aromatic ether **260**. With the C-6 hydroxyl in the natural configuration of (-)-dihydroisocodeine, the crucial radical cascade/C-13 closure was effected by treatment with tin hydride at 130 °C, presumably through the intermediacy of **263**. It is noteworthy that only the vinylthiophenol functionality gave good stereoslectivity in the radical-mediated closures. Similar closures employing other radical acceptors failed to produce single diastereomers. Finally, treatment of **264** with Li/*t*-BuOH produced the nitrogen-centered anion, which closed the E-ring with correct stereochemistry at C-9. Thus, an asymmetric formal synthesis of morphine from (-)-dihydroisocodeine was achieved in 13 steps from *m*-methoxyphenethylamine.



Reagents and Conditions: a) nBu$_3$SnH, AIBN, toluene (30%); b) Li, tBuOH (85%)

Scheme 31. Parker's radical cascade toward the synthesis of dihydrocodeine.

II-3.3 Approaches to Morphine Involving Heck-type Cyclizations

Overman (1993)[5]

Overman's Heck-based strategy was notable in that it was only the second to provide access to either enantiomer in the series of morphine alkaloids- the first enantiodivergent synthesis was reported by Rice in 1980.[126] The convergent design is based on a key intramolecular Heck cyclization of the aryl halide **268** onto its tethered octahydro- isoquinoline, providing the dextromorphinan ring system in **267**. Condensation of allyl silane **269** with aromatic aldehyde **270** afforded the chiral isoquinoline synthon **268**, which was utilized in the strategic palladium-catalyzed cyclization.

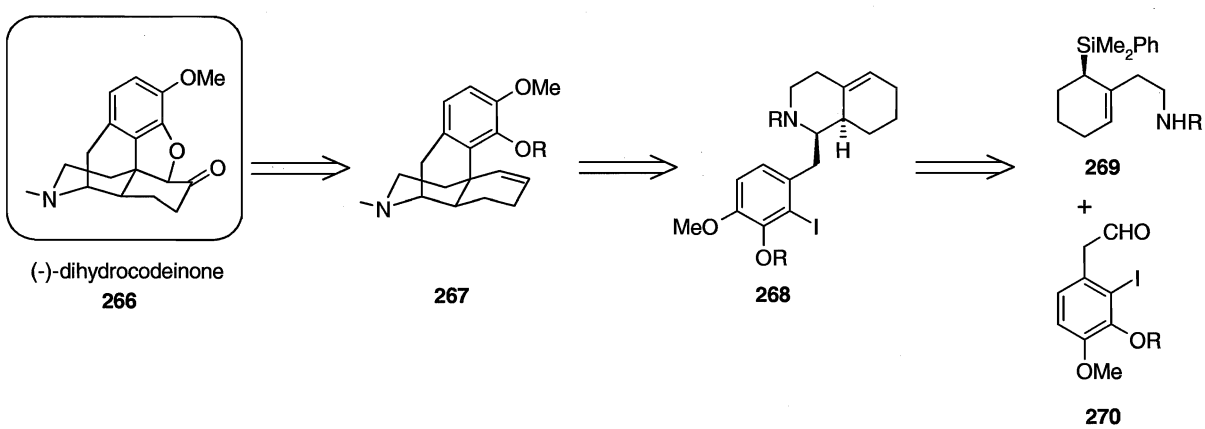
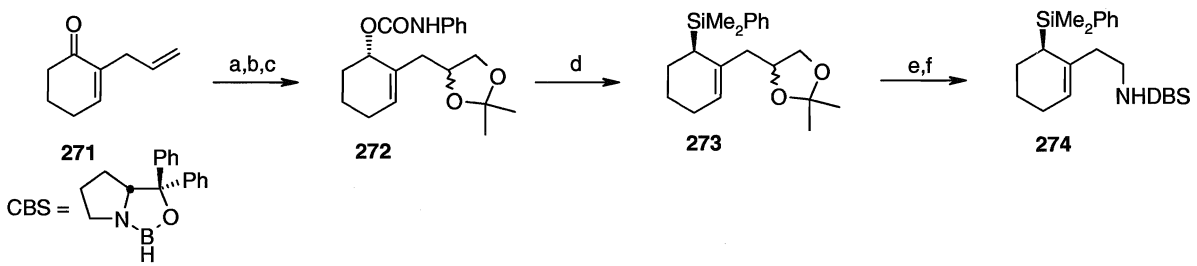


Figure 16. Retrosynthetic analysis of Overman's morphine approach.

For simplicity, the route toward natural morphine is described in Scheme 32.. The synthesis began with an enantioselective reduction of 2-allylcyclohex-2-en-1-one with catechol borane in conjuction with the (*R*)-CBS oxazaborlidine reagent, providing the

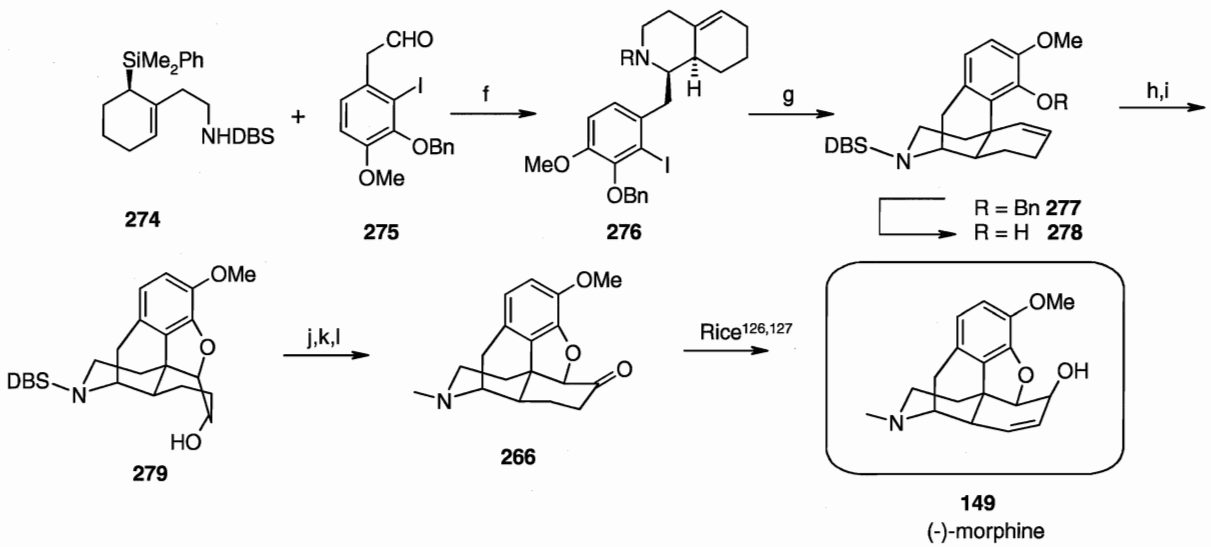
precursor to natural morphine. The resulting enantioenriched alcohol was converted to its carbamate and the olefin transformed to its diol, which was then protected as its acetonide. It is noteworthy that the reduction of **271** using the (*S*)-enantiomer of the CBS oxazaborilidine gives the expected allylic alcohol in similar yield and with comparable enantioselectivity. This enantiodivergent route allows access to both enantiomers of morphine.



Reagents and Conditions: a) CBS, catechol borane, (93%, 96% *ee*); b) phenyl isocyanate (93%); c) OsO_4, R_3NO, acetone, H^+ (78%); d) *n*BuLi, $CuI(Ph_3P)_2$, $PhMe_2SiLi$ (81%); e) *p*TsOH, MeOH, $NaIO_4$, DBS-NH_2 (82%)

Scheme 32. Synthesis of allyl silane **274.**

A suprafacial S_N2' displacement of the carbamate with $PhMe_2SiLi$ in the presence of *n*BuLi and $CuI(Ph_3P)_2$ gave the allyl silane **273** in 81% yield. The diol was liberated and subsequently cleaved to its corresponding aldehyde, which underwent condensation with DBS-NH_2 (dibenzylsuberylamine). Following cyanoborohydride reduction, the amine was condensed with aryl aldehyde **275** in the presence of ZnI_2 to give isoquinoline derivative **276**, Scheme 33.



Reagents and Conditions: f) 5 mol% ZnI_2, EtOH, 60 °C (82%); g) $Pd(TFA)_2(Ph_3P)_2$, 1,2,2,6,6-pentamethylpiperidine, toluene (60%); h) $BF_3.OEt_2$, EtSH (79%); i) CSA, 3,5-dinitroperoxybenzoic acid, CH_2Cl_2, 0 °C (60%); j) TPAP, NMO (86%); k) H_2, $Pd(OH)_2$; l) HCHO, (80% over two steps).

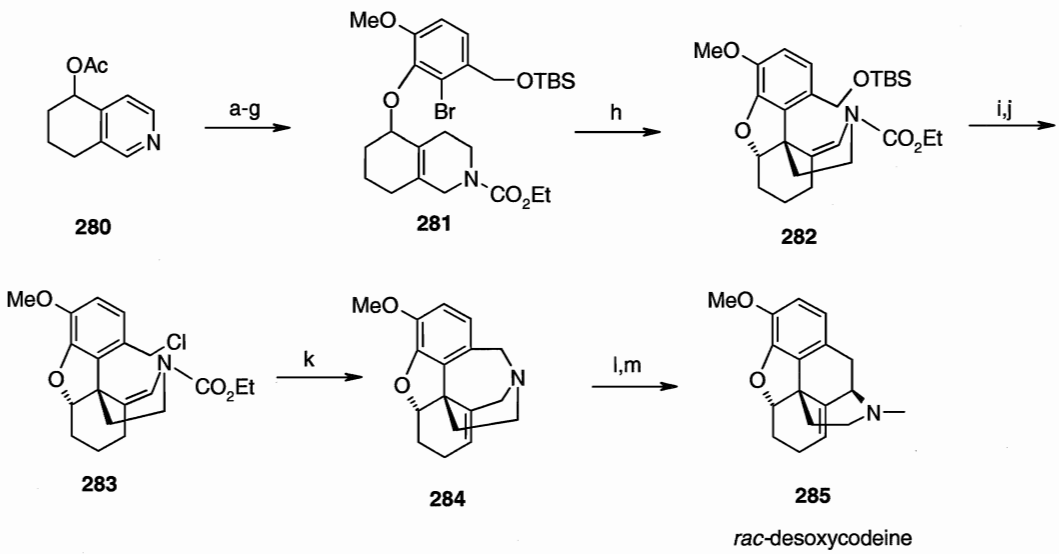
Scheme 33. Overman's Heck cyclization and final transformations to morphine.

The Heck cyclization, critical to the establishment of the C-13 quaternary center, was accomplished by treatment of **276** with 10 mol% $Pd(TFA)(Ph_3P)_2$ in refluxing toluene using 1,2,2,6,6-pentamethylpiperidine as base. The tetracycle **277** having been established, the remaining challenge was the closure of the benzofuran ring. This was carried out by debenzylation to give **278**, and epoxidation of the camphorsulfonic salt of **278,** which gave the dihydrobenzofuran **279** in 60% yield. Oxidation of the resulting alcohol provided (-)-dihydrocodeinone **266**, which was further converted to natural morphine as described by Rice.[126,127]

Cheng (1997)[128]

Cheng reported the synthesis of truncated morphinans through the application of an intramolecular Heck reaction as an alternative to radical cyclizations. Though he originally investigated C-12 -C-13 bond closures by a radical cascade,[129] Cheng maintains that there are several advantages to the use of the Heck reaction over radical reactions, such as the ability to carry out enantioselective closures mediated by chiral ligands and the possibility for further derivatization via the unsaturation unit which results from Heck products.

His initial model studies, designed to provide functionalizable truncated morphinans, led to the development of a total synthesis of racemic desoxycodeine.[130] The key strategy of Cheng's synthesis is the elaboration of isoquinoline, which constitutes the ring-C and D carbon and nitrogen framework, to a Heck cyclization precursor, the product of which reaction provided the C-12, C-13 bond closure. An attempted Pd-mediated olefin cyclization yielded, unexpectedly, gave instead the corresponding *N*-benzylation product. This advanced intermediate was salvaged by a Stevens rearrangement to give racemic desoxycodeine.



Reagents and Conditions: a) MeI, CH_2Cl_2; b) $NaBH_4$, MeOH, (85% over two steps); c) ethyl chloroformate, $KHCO_3$, $ClCH_2CH_2Cl$; d) NaOH, MeOH, (86% over two steps); e) 2-bromoisovanillan, PBu_3, DEAD (85%); f) $NaBH_4$, MeOH (88%); g) TBDMS-Cl, imid (84%); h) $Pd(OAc)_2$, MeCN (62%); i) TBAF, THF (95%); j) NCS, PPh_3, THF (96%); k) $Pd(PPh_3)_4$, MeCN (59%); l) MeI, CH_2Cl_2; m) PhLi, Et_2O.

Scheme 34. Cheng's synthesis of desoxycodeine **285**.

Hudlicky (2001)[7]

Hudlicky realized an elegant approach to the morphine skeleton, whose key step involved a rare Heck cyclization to establish the C-13 quaternary center. A retrosynthetic disconnection shows that the aromatic A ring would be derived from bromoguaicol, Scheme 21. The advanced isoquinoline synthon would ultimately be derived from homochiral bromophenethyl dienediol, available from whole-cell fermentation of the phenethyl bromide. The key Heck coupling precursor **286** would arise from opening of the isoquinoline epoxide **288** with the phenolate anion of bromoguaicol **287**.

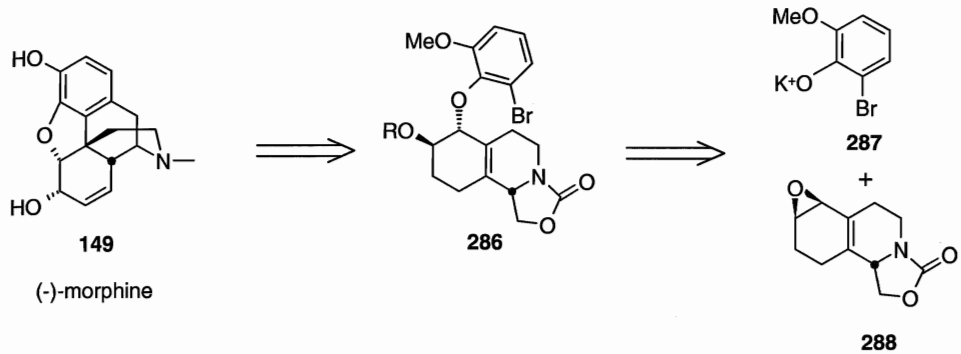
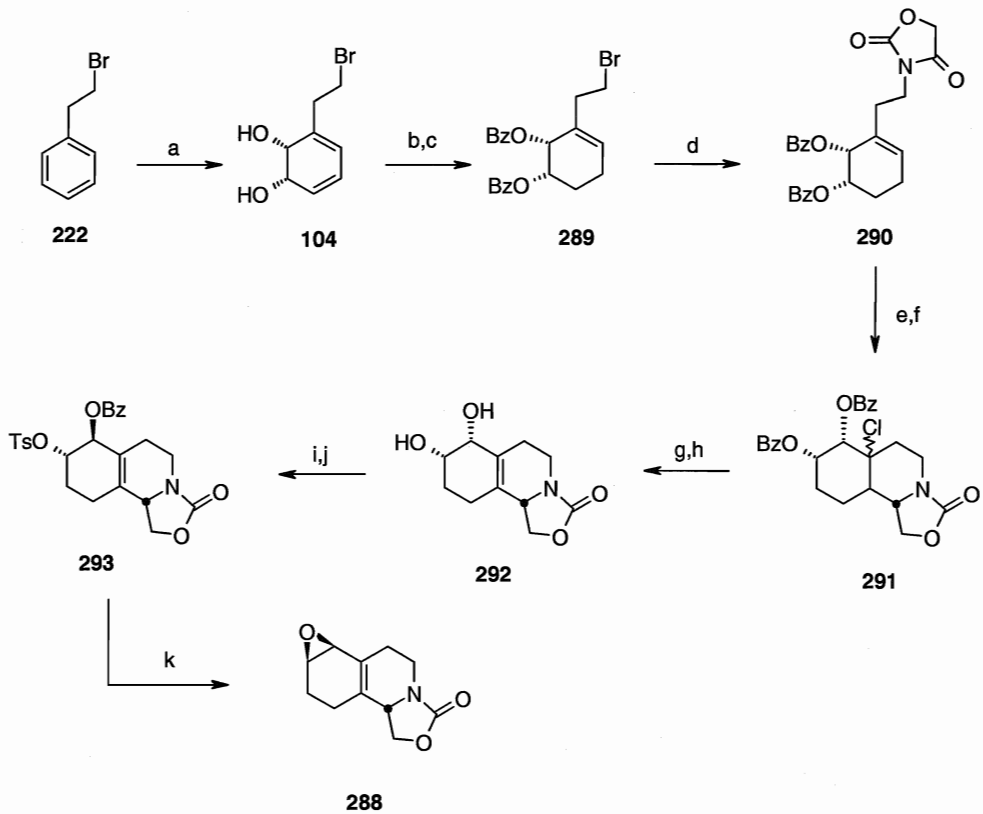


Figure 17. Retrosynthetic analysis of Hudlicky's Heck approach.

The isoquinoline synthon, which makes up the B-C ring systems of morphine, had previously been employed as a 9-carbon carrying unit in the 1996 and 1998 radical cyclization studies directed toward the synthesis of *ent*-morphinans.

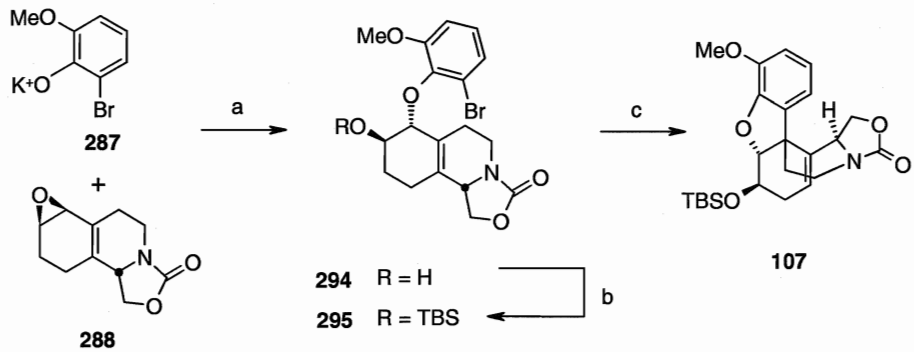
Phenethylbromide **222** was subjected to whole-cell fermentation with *E. coli* JM 109 (pDTG601) to provide the corresponding chiral diene diol **104**. The diol was converted in several steps cyclization precursor, **290**. Treatment of **290** with aluminum trichloride afforded the isoquinoline scaffold through an imimiun ion cycloaddition, the product of which was subjected to dehydration under basic conditions (DBU, 100 °C). At this stage, a key issue is the attachment of the aryl unit at C-5. An initial inversion step was necessary to provide the correct stereochemistry following attachment of the aromatic A-ring by a Mitsunobu reaction.



Reagents and Conditions: (a) *Escherichia coli* JM109 (pDTG601); (10 g/L); (b) potassium azodicarboxylate (PAD), AcOH, MeOH (52%); (c) benzoic acid, DCC, DMAP, (95%); (d) oxazolidine-1,4-dione, tetramethylguanidine, THF (79%); (e) $NaBH_4$, MeOH, THF (quant); (f) $AlCl_3$, CH_2Cl_2, *anti* (16%), *syn* (40%); (g) DBU, DMSO, 100 °C, (16%); (h) NaOMe, THF, (87%); (i) *p*TsOH, py, DMAP, (45%); (j) benzoic acid, nBu$_3$P, DEAD, THF, (79%); (k) NaOMe, THF, (68%).

Scheme 35. Synthesis of Hudlicky's B,C-ring -isoquinoline synthon.

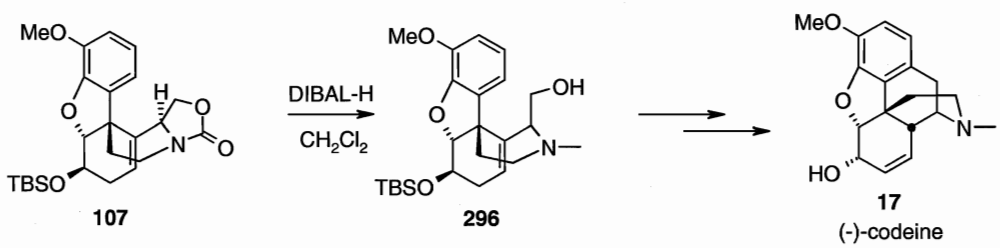
Opening of the epoxide **288** with the potassium salt of bromoguaicol gave the Heck-cyclization precursor having all the necessary carbons in the morphine skeleton. The remaining alcohol functionality was protected as its silyl ether prior to palladium-catalyzed cyclization. Treatment of **295** with $Pd(PPh_3)_4$ in toluene and employing proton sponge® as base gave the cyclized Heck product **106** in 74% yield.



Reagents and Conditions: a) DME, 18-Crown-6, reflux (80%); b) TBS-OTf, CH_2Cl_2, iPr_2EtNH (77%); c) $Pd(PPh_3)_4$, proton sponge™, toluene, reflux (74%).

Scheme 36. C-13 closure facilitated by palladium catalysis.

The oxazolidinone was reduced to give the *N*-methyl functionality in the natural product. A total synthesis of condeinone, and by extension, a formal synthesis of morphine will require closure of the C10-C11 bond, isomerization of the olefin, and inversion of C-6.



Scheme 37. Final transformations toward (-)-codeine.

Trost (2005)[6]

Trost developed a divergent approach in which the key intermediate cyano aldehyde **309** could be transformed into the galanthamine or morphine derivatives. The general strategy relies on two well-developed palladium-catalyzed reactions: the asymmetric allylic alkylation reaction (AAA), which was used to introduce asymmetry, and the Heck

cyclization, through which the C-13 quaternary center was established in both series of natural products.

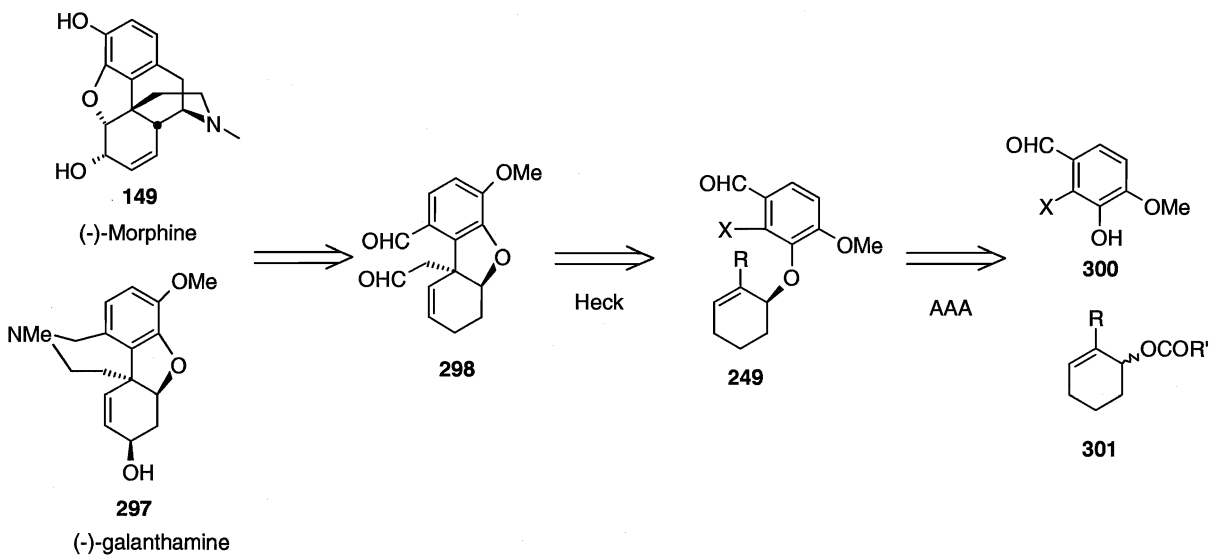
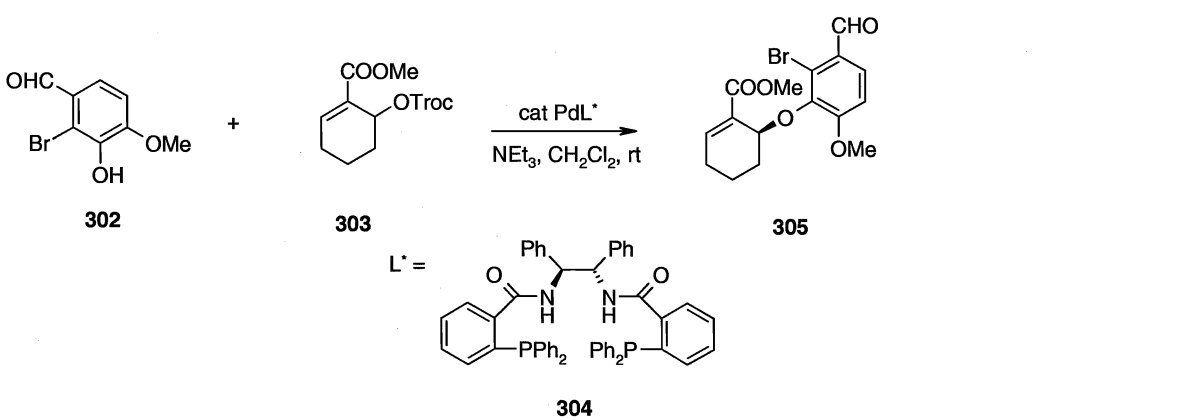


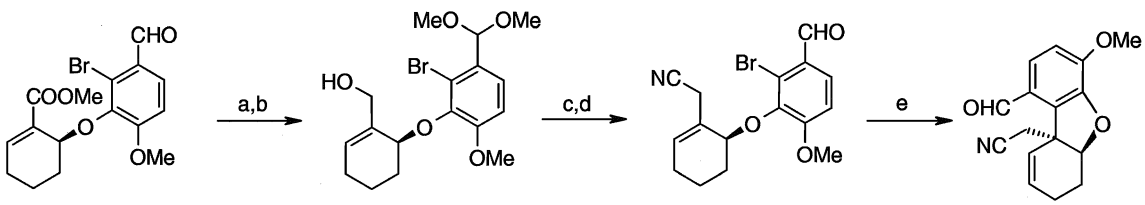
Figure 18. Retrosynthetic analysis of Trost's divergent approach to morphine and galanthamine.

The aryl ether **305** was synthesized by a palladium-catalyzed asymmetric allylic alkylation of allylic carbonate **303** with bromo-isovanillin **302**, affording the aryl ether in 72% yield and 88% *ee* facilitated by *bis*-phosphino ligand **304** shown below, Scheme 31.



Scheme 38. Synthesis of aryl ether **305**.

The ester in aryl ether **305** was reduced to its alcohol after protection of the aldehyde as its acetal. The alcohol was then activated toward displacement with acetonecyanhydrin under Mitsonobu conditions. Treatment of this material with a catalytic amount of *p*-toluenesulfonic acid regenerated the cyano aldehyde, which was subjected to a Heck closure to establish the C-13 quaternary center as detailed in Scheme 40.

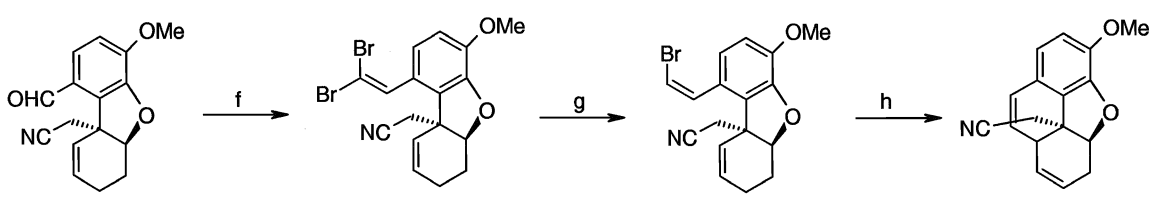


305 **306** **307** **308**

Reagents and Conditions: a) 1.5 mol % *p*TsOH, $CH(OMe)_3$, MeOH; b) DIBAL-H, toluene, -78°C; 85% (over two steps); c) Ph_3P, acetonecyanhydrin, DIAD, Et_2O; d) 2.2 mol % *p*TsOH, THF, H_2O, 76% (over two steps); e) 15 mol % $Pd(OAc)_2$, 15 mol % dppf, 3 equiv Ag_2CO_3, toluene, 107 °C, 91%.

Scheme 39. Heck closure to key intermediate **308**.

A Corey-Fuchs homologation of the aldehyde **308** to its dibromide, and reduction of the dibromide to its *Z*-vinyl bromide set the stage to perform a second Heck closure, which furnished the phenanthrofuran core of the alkaloid.

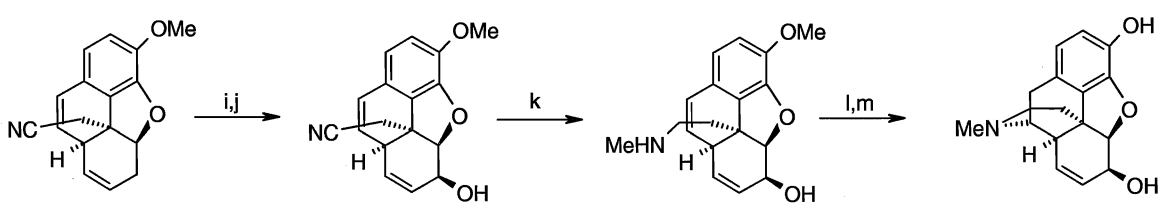


308 **309** **310** **311**

Reagents and Conditions: f) CBr_4, PPh_3, CH_2Cl_2, 91%; g) 5 mol % $Pd(PPh_3)_4$, $n$$Bu_3SnH$, toluene, 88%; h) 15 mol % $Pd(OAc)_2$, 15 mol % dppp, Ag_2CO_3, toluene, 65%.

Scheme 40.

Scheme 41 details the final transformations to morphine, which involved a selenium-dioxide mediated allylic oxidation of C-7 to its enone and subsequent reduction of the enone to its allylic alcohol. Reductive amination of the nitrile was carried out in a one-flask operation by allowing the imine complex to form by reduction of the nitrile in methylene chloride. Ammonium bromide in dry methanol was then added to quench any excess hydride and liberate the free imine. Transamination was effected by addition of excess methylamine and the secondary imine reduced *in situ* to its methylamine derivative by addition of sodium borohydride. The penultimate step in the synthesis of morphine involved a unique photochemical closure of the methylamine anion onto the allylic C-14 center. This step was ultimately carried out by treating compound with 6 equiv of LDA in THF in the presence of a 150-W tungsten bulb. Codeine was converted to morphine by demethylation with BBr_3 according to the procedure of Rice.[131]



311 **312** **313** **149**

(-)-morphine

Reagents and Conditions: i) SeO_2, dioxane, sand, 75 °C; j) DIBAL-H, THF, Et_2O, 99%; k) DIBAL-H, CH_2Cl_2/Et_2O, then NH_4Br, $MeNH_2$, and then $NaBH_4$ (quant); l) LDA, THF, 150-W tungsten bulb, 57%; m) BBr_3,, CH_2Cl_2.

Scheme 41. Trost's final transformations in the synthesis of morphine.

Throughout the 19th and early 20th century, experiments aimed at the structural elucidation of morphine have been closely associated with the development of the discipline of organic chemistry. Today, 54 years after the first synthesis by Gates, morphine remains a formidable target for the synthetic chemist, and new contributions to organic synthesis continue to be made as a result of these pursuits. Now that over thirty formal or total syntheses of morphine have been reported, the next remaining challenge may be even more difficult to attain- a fully synthetic route to morphine that would compete economically with its isolation. To date the most efficient synthesis is that of Rice, which provides a relatively direct route in morphine in 29% overall yield.[126]

The complexity of morphine alkaloids has inspired a number of creative approaches which address the difficult steps common to many syntheses- C-12,C-13 bond connection, the aryl ether formation, etc. The preceding chapter highlights some of the important contributions which feature Diels-Alder, radical cascade, or palladium-catalyzed bond-forming reactions as key strategies in the rapid construction of morphinan alkaloids. However elegant, most of these syntheses are far from ideal. Many suffer from non-selective bond formation at C-9, require either tedious protection/deprotection sequences, and/ or difficult, late-stage C-ring oxygenation protocols. Some of these problems may be addressed in part through judicious choice of starting material.

The arenedihydrodiols which have found application in a variety of enantioselective synthesis are particularly well-suited to morphine synthesis. Not only are the starting material chiral (obviating tedious enantio-enrichment protocols), they are functionally rich. The natural 1,2-disposition of the diol functionality allows easy adaptation of these substates as C-ring morphine synthons, having naturally correct

configuration at C-6, and *ent*-configuration at C-5. This particular arrangement is well suited for Mitsunobu-type coupling of aromatic halides, substrates which may be exploited in radical or Heck-type cyclization reactions. Moreover, the aromatic A-ring may also arise from fermentation of aromatics, as substituted bezenes are readily converted to their corresponding catechols by oxidation with *E. coli* JM 109 (pDTG601).

Radical cascade and Heck reactions, some of which were highlighted by application to morphine synthesis in the previous section, will be re-visited in a chemoenzymatic approach, with the ultimate goal of greatly shortening the length of morphine synthetic sequences. Athough all dienediols harvested from fermentation are functionality rich, we continue to isolate new diol metabolites which may constitute important intermediates in the synthesis of complex molecules, such as the morphine alkaloids.

III Discussion

III-1 Introduction

The present research addresses, as a primary goal, our recent efforts toward the chemical synthesis of morphine alkaloids; several unique approaches to the target molecules are presented. Despite its being one of the oldest drugs on record, morphine (and its derivatives) continue to find new applications in the medical field, such as in open heart surgery and pain control.[132,133] However, only a few specific geographic areas produce opium poppies having usable amounts of these important natural products. The problem is further compounded by the fact that many of these countries suffer from political turmoil. The ultimate goal of the Hudlicky research group is to design a

synthesis of morphine, beginning from enzymatically generated starting materials, which would rival the cost of isolation from its natural source. Such a goal would ensure access to steady supplies of the natural product without dependence on the isolation from its natural source.

As target molecules have become increasingly complex, chemists have enlisted a variety of "borrowed" technologies that have resulted in greatly shortened and improved overall efficiency of many syntheses. For example, the incorporation of enzymatic reactions (traditionally of interest to the biochemist or biologist) into synthetic sequences can provide chiral synthons that may be further converted into a variety of beneficial products. Among these materials are natural products which are known to possess medicinal properties. A major component of our program is aimed at the synthesis of morphine alkaloids and other medicinally useful natural products starting from materials which are obtained through oxidative fermentation of aromatic compounds. Two approaches to the synthesis of morphine alkaloids will be discussed. The first approach targets thebaine, and the key strategy hinges on the ability to chemically or enzymatically oxidize the divalent sulfur in substituted thiophenes. Fittingly, this approach will be discussed only after the work involving enzymatic oxidation of aromatic substrates, including a series of compounds bearing divalent sulfur functionalities. The second approach to morphinans is based on radical and palladium-mediated bond-forming reactions. The common thread to this work is the use of the dienediol nucleus derived from oxidation of aromatics. Preceding the discussion of these two major approaches will be a summary of the research addressing the substituent tolerance and substrate specificity by the enzyme toluene dioxygenase.

A cursory glance at Table 1 reveals that the diols derived from benzene, chlorobenzene, bromobenzene, and toluene have enjoyed broad application in the synthesis of structurally-diverse natural products. Although these four synthons remain important building blocks, we continue to search for new metabolites with increased functional content. It is because the enzyme toluene dioxygenase exhibits a high tolerance for functionally diverse substrates that we are able to access new metabolites from fermentation. Part of the present work is devoted to the isolation and rigorous characterization of new metabolites from fermentation. To this end, a series of bromothioanisoles was prepared and subjected to oxidation. Diene-diols such as **316** may be amenable to further manipulation. Elaboration of metabolite **316** by attachment of olefinic tethers would allow investigations into radical or Heck-cascade reactions onto the vinylbromide. Additionally, the vinyl sulfone may be used in conjugate addition reactions. Specifically,our efforts to use derivatives of metabolites such as **316** in Diels-Alder studies will be described in III-2.0. The oxidation of this series of thioanisoles, thus, served as a model for the tandem oxidation of thiophene-Diels-Alder approach toward thebaine.

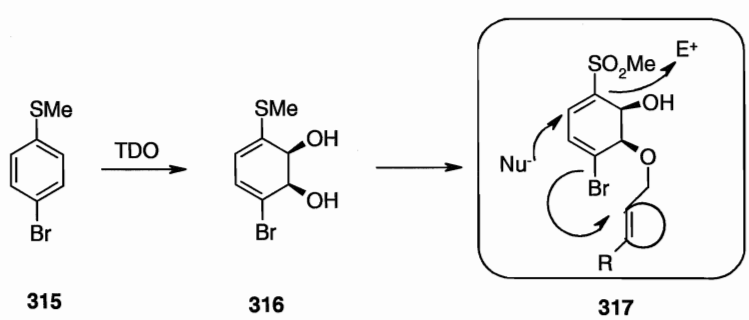


Figure 19. Reactive options in dienediol **317**.

m-Dibromobenzene is unique in that its corresponding aromatic diol is the only *m*-substituted arenediol to have been used in a total synthesis effort.[3] The results of whole-cell oxidation of the remaining isomers comprising this series, the ortho- and para-substituted dibromides, are the next to be presented. Figure 20 highlights the synthetic utility of the *o*-dibromobenzenediol in the projected synthesis of cyclitols and carbohydrates.

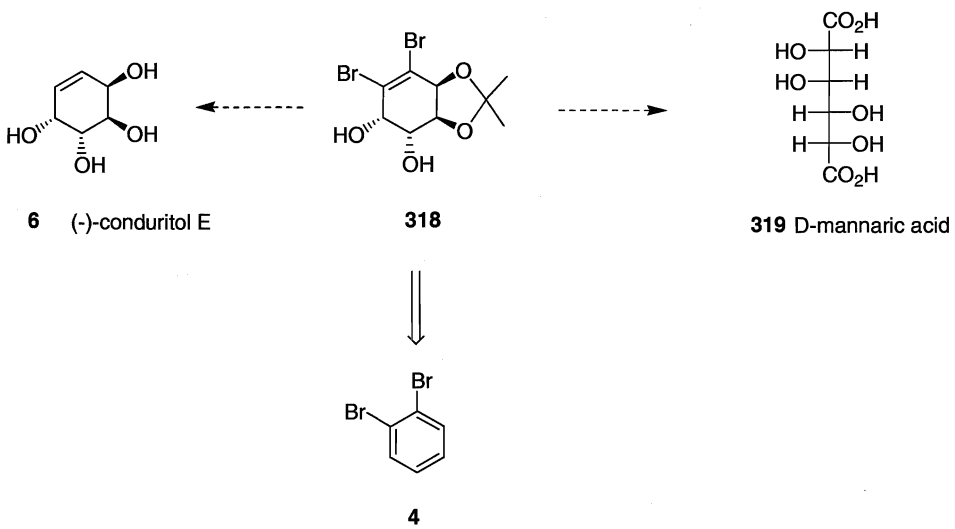


Figure 20. Access to sugars and cyclitols from halobenzenes.

The outcome of oxidation for each substrate will be discussed with regard to its symmetry. Additionally, the opportunities for selective conversion of *o*-dibromodienediol to either sugars, such as D-mannaric acid, or cyclitols, such as conduritol E, will be highlighted.

The epoxide and aziridine derivatives of cyclitols are invaluable synthons for natural product synthesis. As shown in Table 1, the cyclitol or aminocyclitol moiety is a feature common to many natural products, and one readily accessible from the fermentation of aromatic substrates. The nucleophilic opening of cyclitol epoxides or

aziridines thus provides a means to elaborate these useful synthons. We initiated a program directed at using silica gel as a replacement technology to metal or acid-mediated opening of strained heterocycles, such as epoxides and aziridines. The results of our research in this area will be presented in Chapter III-5.0.

Cyclopropylbenzene, previously shown to be excellent substrates for the enzyme, was originally investigated as part of a mechanistic study of toluene dioxygenase.[134] As part of our ongoing interest in the mechanism of this enzyme, the results of oxidation of a series of cyclopropylbenzenes will be presented. The study, which includes a number of cyclopropylbenzenes bearing remote chiral centers, is aimed at answering the important question of whether or not toluene dioxygenase is capable of resolving pro-chiral centers proximal to the site of oxidation on the ring. In addition to the provision of chiral vinylcyclopropanes, often used in tandem cycloaddition processes, the study should present a clearer picture of the specificity of the enzyme for its substrates.

In connection with our long-standing interest in the oxidation of aromatic and sulfur-containing compounds, we present a new morphine approach whose key step would rely on a tandem enzymatic sulfoxidation-Diels-Alder sequence. Chiral sulfoxidation of thiophenes, which occurs with concomitant loss of aromaticity, is a reaction that is unique to the world of enzymes.

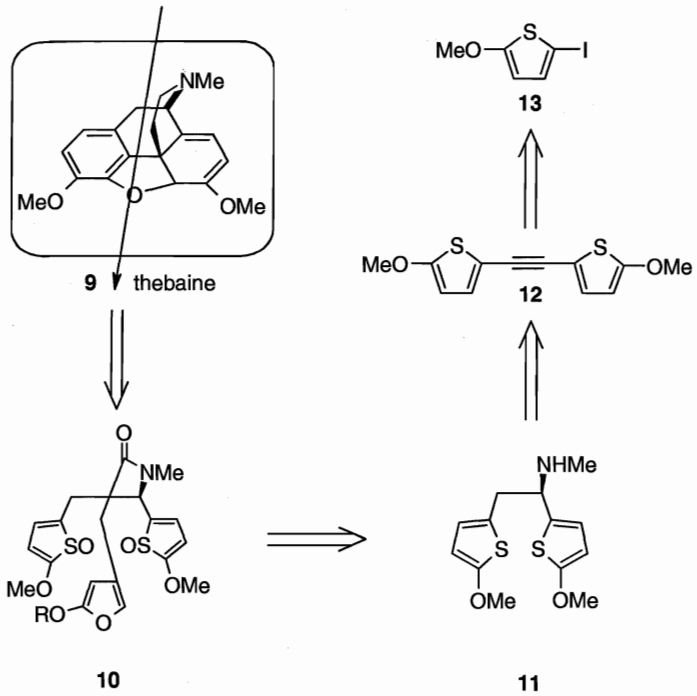


Figure 21. Retrosynthetic analysis of thebaine synthesis.

As only limited examples of such enzymatic reactions are described in the literature, we initially embarked on a model study directed at establishing the feasibility of such tandem reaction. Our efforts toward the construction of this skeleton based on simple model studies are detailed in Chapter III-6.1.

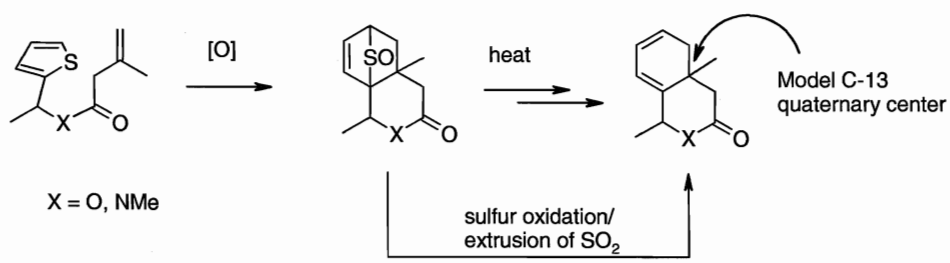


Figure 22. Model approach involving tandem sulfoxidation/Diels-Alder cyclization.

This approach would allow rapid construction of the pentacycle from relatively simple achiral precursors. In connection with our interest in aromatic sulfur oxidations, we

examined the oxidation of a variety of substrates bearing a divalent sulfur functionality; the results of these general studies are detailed in Chapter III-3.1.

The second major approach to the morphinan skeleton is aimed at the introduction of the aromatic A-ring through palladium catalysis. This new approach promises several advantages over previous routes. As discussed in the historical section, a number of morphine syntheses rely on a Mitsunobu alkylation for introduction of the aromatic A-ring to an oxygenated C-ring. This disconnection necessitated a number of lengthy inversion and/or protection and deprotections steps when applied to chiral diols from fermentation. By direct alkylation with an aromatic piece, we may avert lengthy inversion steps and correctly set the C- 14 stereocenter with complete control. The discussion section will end with a description of this approach to the current stage of the project.

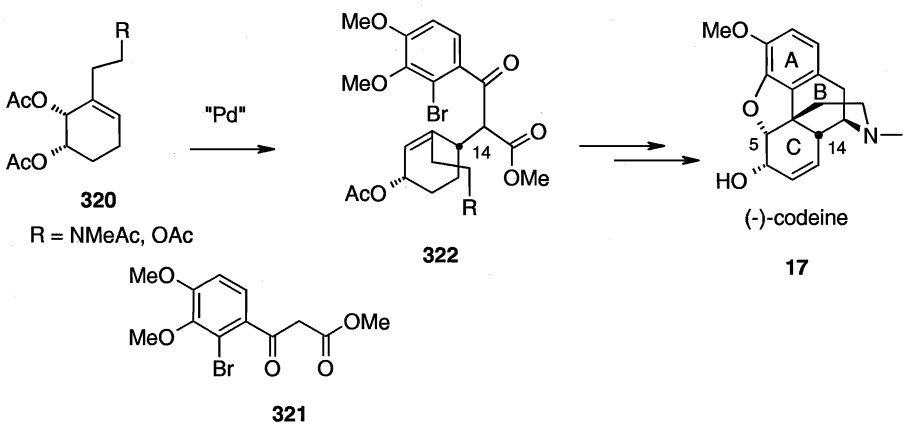


Figure 23. Palladium-catalyzed bond-formation in morphine synthesis.

III-2 Oxidation of Sulfur-containing Aromatic Substrates by Toluene Dioxygenase

The dioxygenase enzymes capable of converting aromatics to their corresponding arene-dihydro dienediols have shown extraordinary selectivity in the oxidation of sulfur-containing aromatics to their chiral sulfoxides, in many cases without accompanied over-oxidation or dihydrodiol formation. Although the exact mechanism for theoxidation is unknown, oxygen uptake experiments with purified dioxygenase enzymes have shown unambiguously that these enzymes are responsible for this transformation.[135]

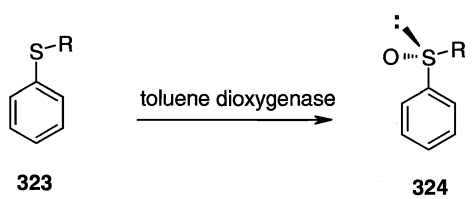


Figure 24. Oxidation of thioanisole to give *R*-sulfoxide.

Although chiral oxidations at sulfur are common to many microorganisms, dioxygenases are known to have an increased level of specificity. Toluene dioxygenase shows a preference for the formation of the *R*-isomer, whereas naphthalene dioxygenase gives predominantly the *S*-isomer.

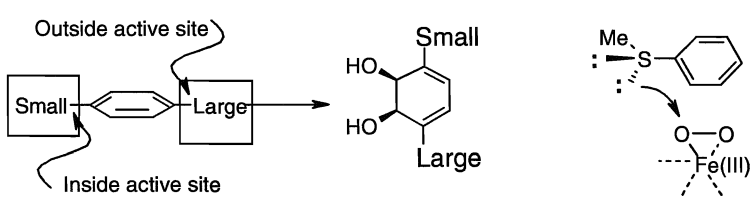
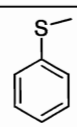
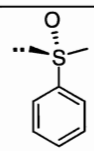
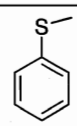
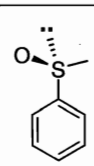
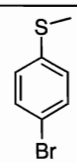
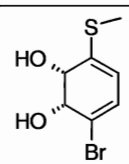
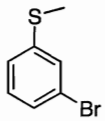
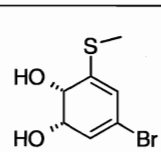
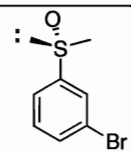
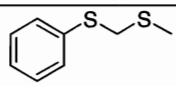
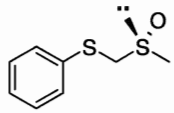
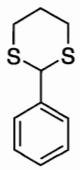
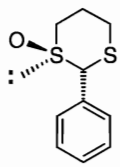
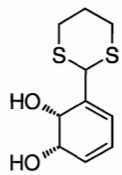
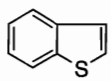
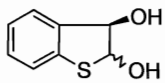
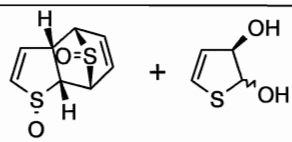
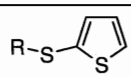
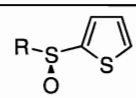
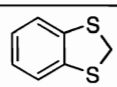
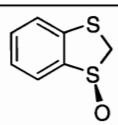


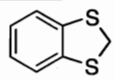
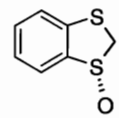
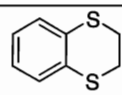
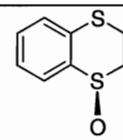
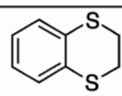
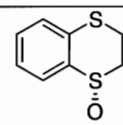
Figure 25. Apparent difference in mechanism for ring vs. sulfur oxidation.

Boyd has proposed a general empirical model for the oxidation of substituted aromatics, which indicates that the larger of the two groups lies distal to the iron center in the active site.[4] While this working model is applicable to a vast number of substituted aromatic substrates, the picture is somewhat more complicated for compounds bearing sulfur functionalities as shown in Figure 25. In cases where divalent sulfur is oxidized to its sulfoxide by dioxygenase enzymes, the thioether must necessarily occupy a position proximal to the iron center of the active site of the enzyme. That sulfur-containing compounds are oftentimes oxidized to chiral sulfoxides with such specificity is more remarkable.

Table 3. Selected Examples of Dioxygenase -mediated Divalent Sulfur Oxidation.

Entry	Aromatic substrate	Metabolite	Organism (Ref)
1	 **323**	 **324**	*Pseudomonas putita* UV4[141] *E. coli* JM 109 (pDTG601)[136]
2	 **323**	 **325**	NCIB 8859 (NDO)[137]
3	 **315**	 **316**	*Pseudomonas putita* UV4[138] *E. coli* JM 109 (pDTG601)[136]

4	 **326**	  **327** **328**	*E. coli* JM 109 (pDTG601)[136]
5	 **329**	 **330**	*Pseudomonas putita* UV4[139]
6	 **331**	  **332** minor **333** major	*Pseudomonas putita* UV4[140]
7	 **334**	 **335**	*Pseudomonas putita* UV4[141]
8	 **336**	 **337** **338**	*Pseudomonas putita* UV4[142]
9	 **339**	 **340** R = Me **341** R = Ph **342** R = 2-Thiophene	*Pseudomonas putita* UV4[142]
10	 **343**	 **344**	*Pseudomonas putita* 9816/11(NDO)[143]

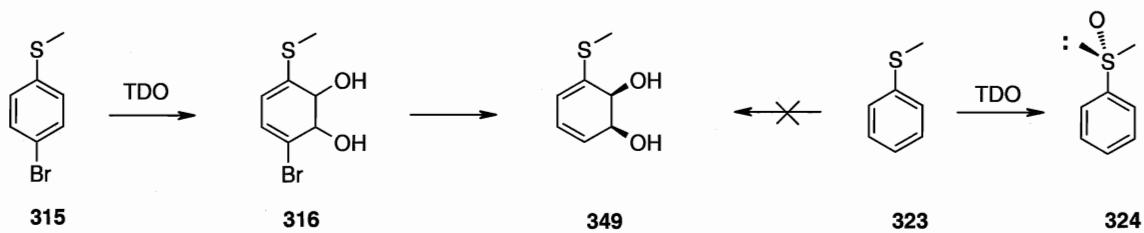
11	 **343**	 **345**	*Pseudomonas putita* UV4[143]
12	 **346**	 **219**	*Pseudomonas putita* 9816/11(NDO)[143]
13	 **346**	 **348**	*Pseudomonas putita* UV4[143]

Despite the overwhelming number of examples in which aromatic thioethers are processed to sulfoxides, there are also many cases in which dioxygenases prefer to give ring-hydroxylated products, without attendant oxidation at sulfur. An interesting case is encountered in thioanisoles. The parent compound, thioanisole, gives exclusively the *R*-sulfoxide in greater than 90% optical purity when subjected to oxidation with toluene dioxygenase, in contrast to *p*-halothioanisoles, which give dihydroxylated products.

In 2004, Boyd published[138] the results of a toluene dioxygenase-mediated oxidation study involving series of para-substituted thioanisoles. In all cases, the oxidation proceeded with high *ee*'s (>90%) to give the corresponding diene diols.

We were initially interested in the specificity of oxidation with respect to substitution patterns on the ring. Our study began with *p*-bromothioanisole **315**, which was converted to its corresponding diene diol **316** in a high yield (3.2 g/L) without any indication of accompanied sulfoxide formation, Scheme 42. We then set out to establish the absolute configuration of the new metabolite. Our initial hope was that we could

isolate a small amount of the corresponding diene diol from the oxidation of thioanisole. This compound was specifically chosen because mono-substituted compounds give exclusively the 2,3-diol with β-stereochemistry, with exception paid to benzoic acids, which give ipso-substitution. Dehalogenation of metabolite **316** would provide a chemical match for comparison.



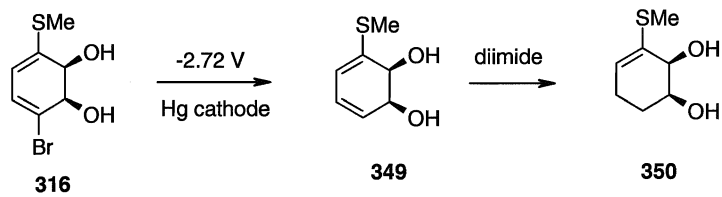
Scheme 42. Initial approach for determination of absolute configuration.

Fermentation of thioanisole **323** gave, instead, exclusively 92% optically pure *R*-sulfoxide **324** and the initial approach was abandoned. The second chemical matching strategy relied on a 1998 report from the Boyd group, which describes the displacement of bromide by treatment with sodium thiomethoxide in HMPA, Scheme 43.[144] We opted to initially reduce diene **72**, whose absolute configuration is well established, to its more stable mono-ene with diimide and subsequently displace the bromide functionality based on analogy to Boyd's experiment.

Scheme 43.

In preparation to make a chemical match, the vinyl bromide functionality on diene diol **316** was reduced electrochemically by Dr. Petr Cankař, and the crude product from

electrochemical reduction submitted directly to diimide reduction, giving vinyl thioether **350**.



Scheme 43. Electrochemical reduction of diol metabolite **316.**

Bromodiene diol **72** was reduced with diimide to vinyl bromide **351**, which was subjected to the conditions (NaSMe, HMPA, 60 °C) employed by Boyd in the synthesis of thioether **349**. We were surprised to find that the physical and spectral properties of vinyl thioether **350** made by electrochemical reduction and subsequent diimide reduction *did not match* those of the compound prepared from bromodiene diol. Their elemental compositions were, however, identical.

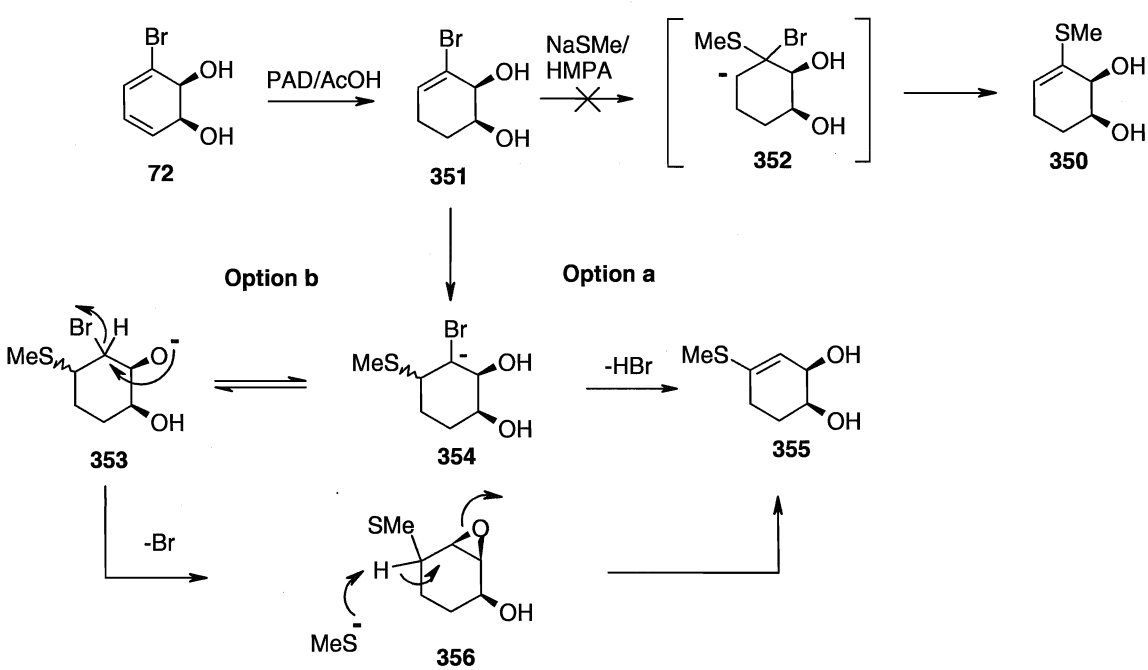


Figure 25. Mechanistic options for rearrangement of compound **351**.

Careful analysis of the COSY NMR spectra of both compounds revealed that a rearrangement had taken place in the course of the sodium thiomethoxide/HMPA displacement of bromide **351**. Two plausible mechanistic options are offered in Figure 25. One can easily assign the structure of the rearrangement as compound **355** based on an analysis of the ^{1}H NMR and COSY spectrum.

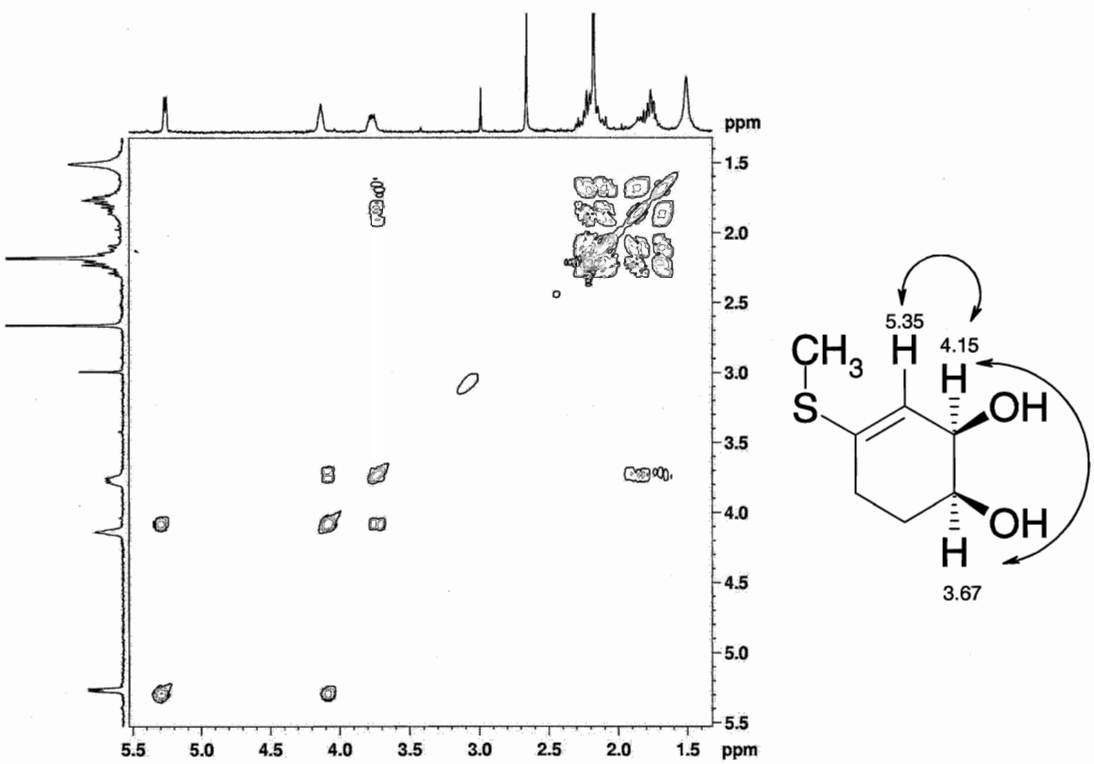


Figure 26. COSY-spectrum of rearrangement product **355**.

The ^{1}H NMR spectrum reveals that the vinyl proton δ 5.35 ppm is a doublet with coupling constant, J = 4.3 Hz. It exhibits a strong coupling with its neighboring proton, which appears at δ 4.15 ppm. The proton at 4.15 ppm, in turn, couples strongly with its neighboring proton at δ 3.67 ppm. The assignment of compound **355** was based of the

characteristic coupling pattern of three contiguous protons, as shown in Figure 26.

Assignment of the regioisomeric structure having identical elemental composition derived from *p*-bromothioanisole is again based on analysis of the ^{1}H NMR and COSY spectra. The vinyl proton at δ 5.61 ppm is a clean triplet with coupling constant J = 3.9 Hz. While the proton at δ 4.10 ppm couples strongly to its neighbor at δ 3.65 ppm, its coupling to the vinyl proton at 5.61 ppm cannot be detected. This characteristic coupling pattern is indicative of structure **350**, in which coupling from the proton at 5.61 ppm to the proton at 4.10 ppm is insulated by the thiomethyl group.

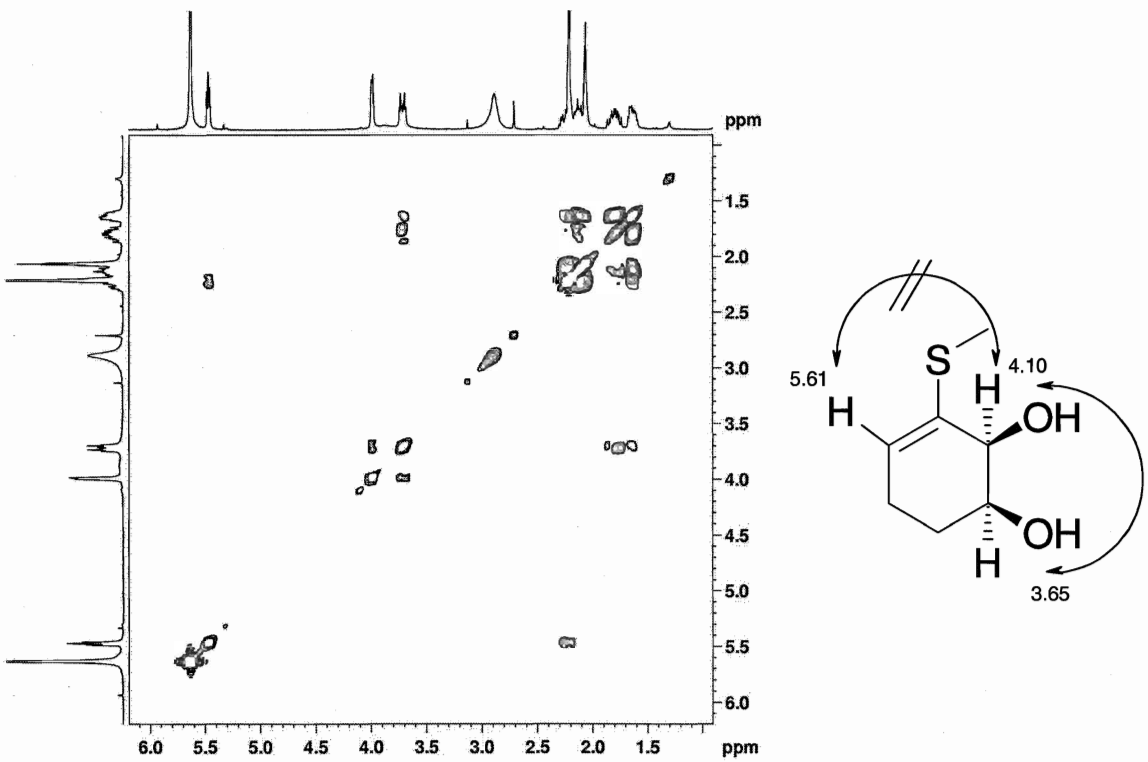
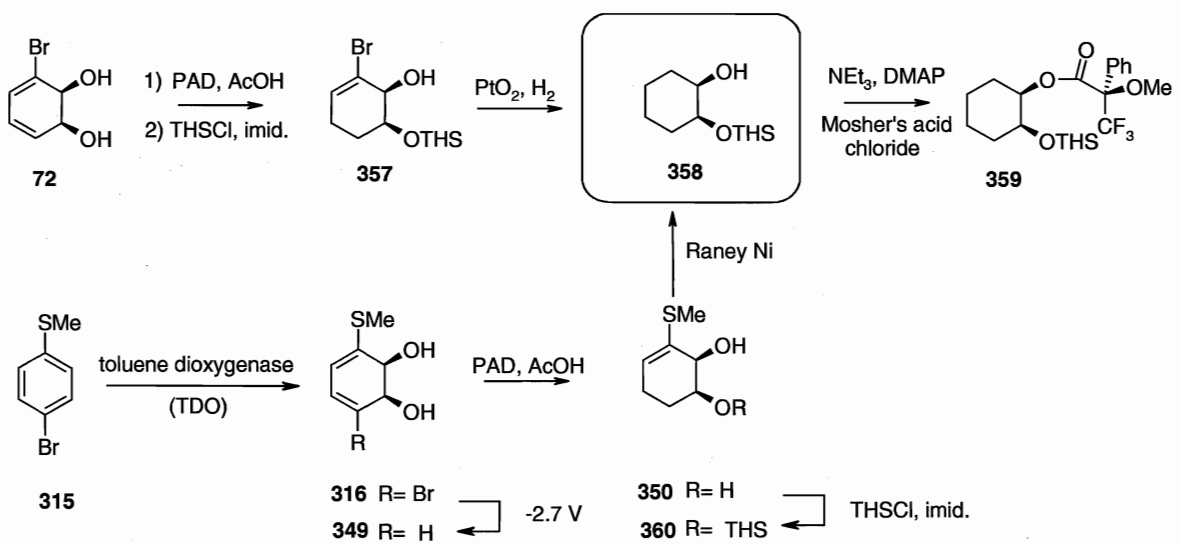


Figure 27. COSY spectrum of compound **350**.

The determination of absolute configuration of diol metabolite **316** was ultimately made by conversion of this compound and bromodiene diol **72** to a common

intermediate, mono-protected silyl ether **358**. Diimide reduction of bromodiene diol **72** and subsequent protection of the distal hydroxyl as a THS silyl ether gave compound **357**, which was subjected to hydrogenation over Adams' catalyst to give mono-protected silyl ether **358**. This intermediate was alternatively synthesized from diol metabolite **316** by electrochemical reduction, and treatment of the crude electrochemical reduction product with diimide to give compound **350**. Diene diol **349** was quickly purified by chromatography on deactivated silica gel for the purpose of characterization, however, the half-life of this compound in pure state at room temperature is less than 20 minutes and it is recommended that it be directly converted to its more stable derivative **350**.



72 **357** **358** **359**

315

316 R= Br
349 R= H

350 R= H
360 R= THS

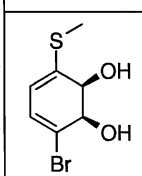
Scheme 44.

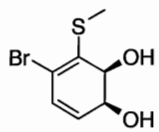
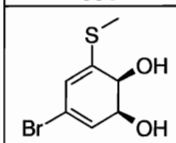
Thioether **350** was similarly protected as its silyl ether, and the resulting compound **360** subjected to reduction by Raney nickel to give the mono-protected diol **358**. Spectral and physical properties of compound **358** prepared by both routes were in agreement. The absolute configuration was determined to be the same for both compounds based on their having the same sign of specific rotation. Determination of *ee* was carried out by

acylation of compound **358** with Mosher's acid chloride. A racemic standard of **359** was initially prepared by treating *rac*-**358** with Mosher's acid chloride. Comparison of the respective acylation products **359** derived from bromodiene diol **72** and diol metabolite **316** revealed that both exist as single diastereomers, indicating that both had been oxidized enzymatically to give a single enantiomeric product.

Having established the absolute configuration and *ee* of compound **316**, we were prompted to undertake a specificity study of the remaining two members of the bromothioanisole series. The ortho-substituted thioanisole was subjected to small-scale fermentation with *E. coli* JM 109 (pDTG601) to give a mixture of the chiral diol and (R)-sulfoxide, with a preference for the diene diol. *m*-Bromothioanisole was also oxidized with the same organism, which gave, in this case, primarily the (R)-sulfoxide along with a small amount of chiral diene diol. We required a larger amount of this diene diol for a chemical proof of absolute configuration and repeated the oxidation on fermentor scale, however, in this case, the oxidation resulted solely in the formation of the sulfoxide, Table 4.

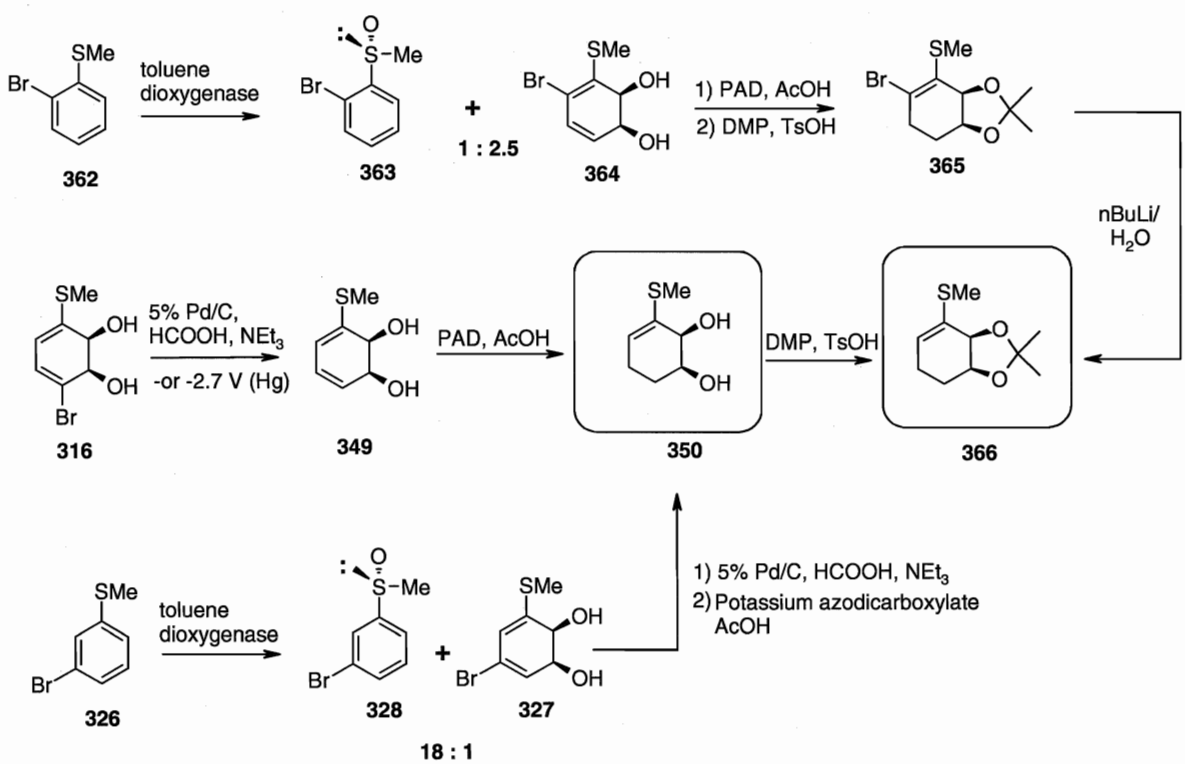
Table 4. Comparison of yield and distribution of products from shakeflask and fermentor transformations.

	Fermentor		**Shakeflask**	
	sulfoxide mg/L	**diol (mg/L)**	**sulfoxide mg/L**	**diol (mg/L)**
 **316**	0	2300	-*	-*

 **364**	50	175	47	117
 **327**	150	0	130	7

*Not performed.

The corresponding chiral sulfoxides are known compounds, and their optical purities were calculated relative to specific rotations reported in the literature.[145,146,147] A chemical proof of absolute configuration of the diene diols was carried out according to Scheme 45.



Scheme 45. Proof of absolute configuration for diol metabolites **327** and **364**.

The distal olefin in *o*-bromothioansiole diol **364** was reduced using diimide and the *cis*-diol functionality protected as its acetonide to give compound **365**. The bromine functionality was removed by lithium halogen exchange followed by an aqueous quench, to provide vinyl thioether **366**. This compound was also prepared from diol **316** by the electrochemical reduction/diimide sequence desribed earlier and subsequent protection of the diol as the acetonide. Spectral data and specific rotations of **366** prepared by both routes were in agreement.

Since diol metabolite **327**, derived from *m*-bromothioanisole, was formed in a extremely low yield, the chemical sequence to determine the absolute configuration had to necessarily be brief. The diol **327** was converted to thioether **350** by a Pd-catalyzed formate reduction, originally described by Heck,[148] followed by diimide reduction. Owing to the small amount of **327** available from *m*-bromothioanisole, an accurate determination of optical purity was not possible. The shared sign of specific rotation of compound **350**, prepared by either route, indicates that the absolute configuration is as shown in Scheme **45**.

We were originally intrigued by the various reactive possibilities available in compounds derived from diol metabolite **316**, such as the sulfone **317**, shown in Figure 28. In addition to the Diels-Alder pathways common to all diene diols, compounds such as **317** can easily be elaborated by Heck or radical cascades from the vinyl bromide to tethered olefins. Additionally, the vinyl sulfone may be exploited in conjugate addition reactions. The fact that each carbon atom could be selectively functionalized made **317** an attractive target for asymmetric synthesis.

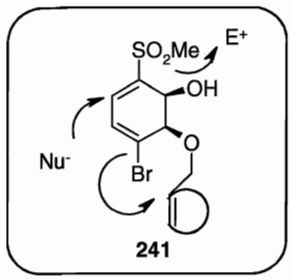
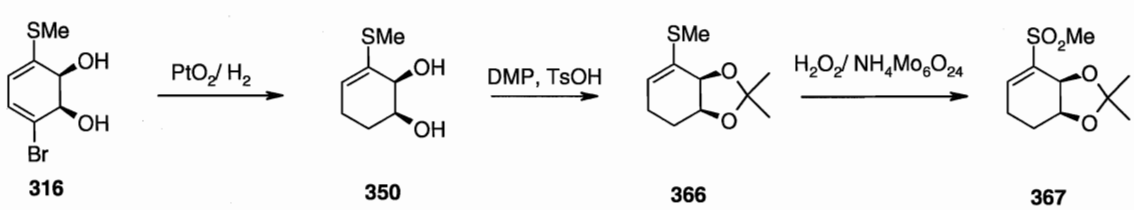


Figure 28. Various reactive options in sulfur-containing diols.

We chose initially to investigate the possibility of Diels-Alder reactions in which the vinyl sulfone would serve as the ene component. These studies were performed with the help of graduate student Jon Collins (Brock University). To this end, thioether **316** was chemically oxidized to its more stable sulfone. Having found conditions which allow oxidation of the thioether directly to the sulfone, we reduced the vinyl bromide of diol **316** by hydrogenation over Adams' catalyst and the resulting compound **350** was subsequently protected as an acetonide, Scheme 46. Oxidation of divalent sulfur to its sulfone was accomplished by treatment with aq hydrogen peroxide and ammonium molybdate. The vinyl sulfone would allow us to investigate Diels-Alder reactions with various diene components.

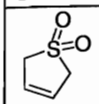
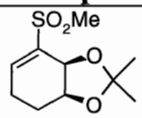
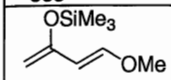
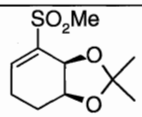
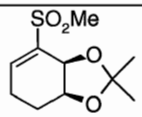


Scheme 46. Synthesis of vinyl sulfone **367**.

Ultimately, the sulfone would serve as a prelude to the tandem oxidation-Diels-Alder sequence that was planned for the synthesis of thebaine. Several dienes were enlisted for

the Diels-Alder studies, however, starting material was quantitatively recovered in each reaction and further elaboration of diol metabolite **316** was abandoned.

Table 5. Attempted Diels-Alder reactions of sulfone 367.

Diene[a]	Dienophile	Solvent	Temperature	Result
 **368**		neat	120 ^{0}	recovery of SM
 **369**		toluene -or- neat	120 ^{0}C	recovery of SM
 **370**		neat	40 ^{0}C to 120 ^{0}C	recovery of SM

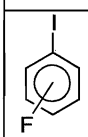
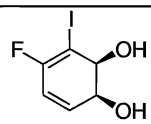
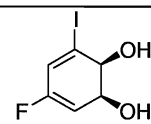
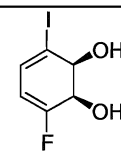
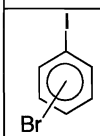
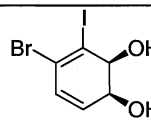
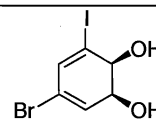
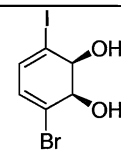
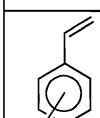
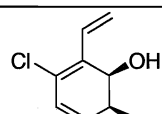
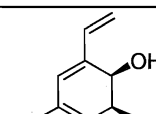
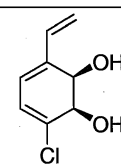
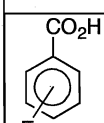
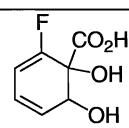
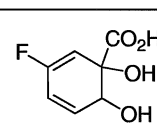
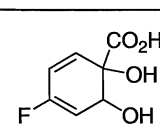
[a] Or diene equivalent

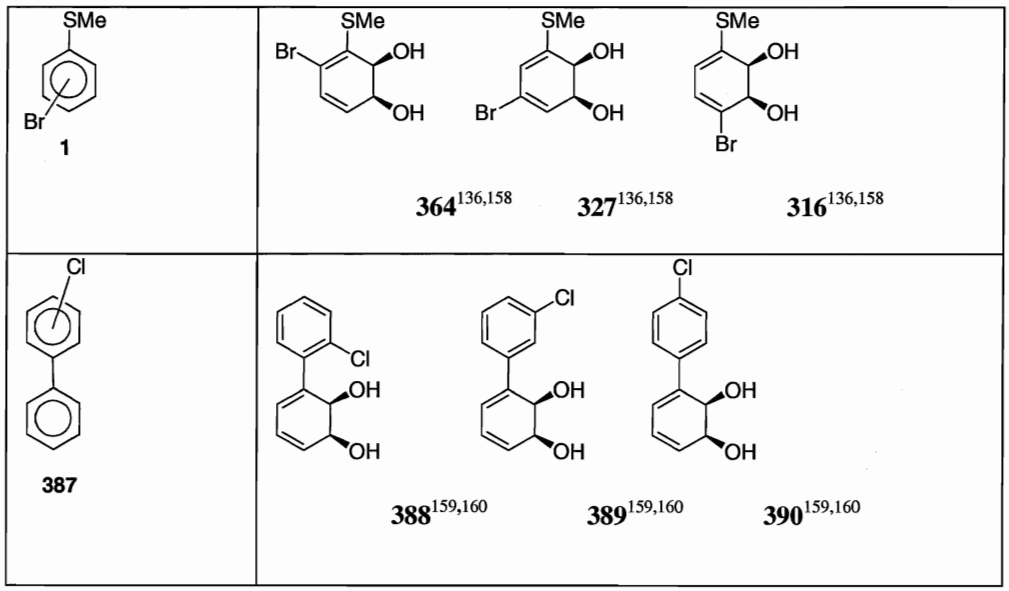
In conclusion, a substrate specificity study with regard to outcome of enzymatic oxidation has been conducted on a series of thioanisoles. The product distribution seems to be highly influenced by the distance between the substituents. In the case of *p*-bromothioanisole, the dienediol **316**, obtained as a single enantiomer, was the exclusive product of oxidation. Moreover, the fermentation of *p*-bromothioanisole with *E. coli* JM 109 (pDTG601) provides useful amounts of the bacterial metabolite, which may be amenable to further application in asymmetric synthesis. Conversion of this metabolite to sulfone **367** has permitted a preliminary Diels-Alder study featuring several commercially available diene components. While these substrates failed to react under our conditions, future work might include a study of substrates having an intramolecular dienyl tethers. The conditions used to effect both chemical and enzymatic oxidation at sulfur will be re-applied to the tandem oxidation/Diels-Alder study toward the synthesis of thebaine.

III-3 Oxidation of o- and m-Dibromobenzene- Synthesis of (-)-Conduritol E.

As an extension to our continued studies concerned with the relationship with the specificity and mechanism of oxidation of aromatics by toluene dioxygenase, we became interested in the fate of oxidation for all isomers of disubstituted aromatics- ortho, meta-, and para. Table 6 lists such a series for which the metabolites are known for all three isomers.

Table 6. Known arene diol metabolites listed by complete series.

Substrate	Products (references)
 **371**	 **372**[149]  **373**[149]  **374**[149,150]
 **375**	 **376**[149]  **377**[149]  **378**[149,151]
 **379**	 **380**[152,153]  **381**[152]  **382**[152]
 **383**	 * **384**[154,155,156]  * **385**[157]  * **386**[154,155,157]



*Absolute stereochemistry not determined.

Meta-substituted aromatics are generally poor substrates for the enzyme, if they are oxidized at all. A notable exception is *m*-dibromobenzene, which gives up to 4 g/L of the corresponding diene diol and was used as chiral starting material in the synthesis of narciclasine.[161] The inherent symmetry in this molecule allows the formation of only a single diene diol, Figure 16.

We decided to investigate the oxidation of the two remaining members of this series of di-bromobenzenes. *p*-Dibromobenzene **392** was oxidized to its corresponding diene diol **393** in 55 mg/L in a small-scale shakeflask fermentation. Although this particular compound is meso, it may find application in asymmetric synthesis through further lipase resolution and desymmetrization.[162] Such procedures have been used to enrich enantiomeric excesses of those diols that are produced as scalemic mixtures.

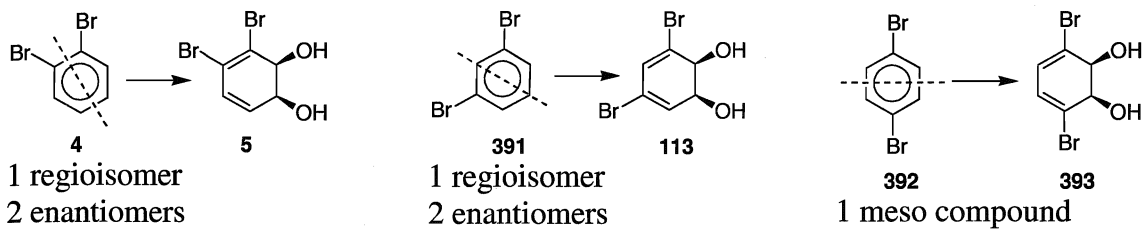
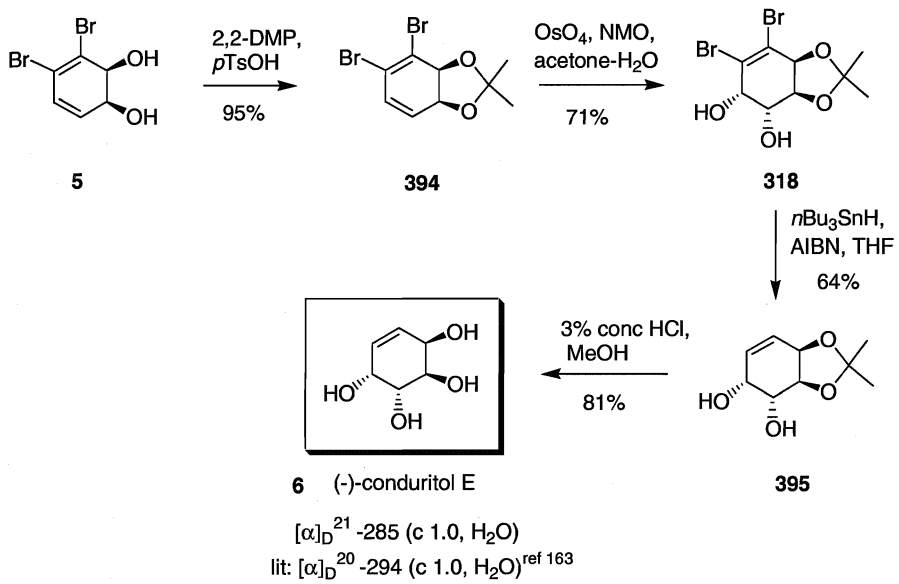


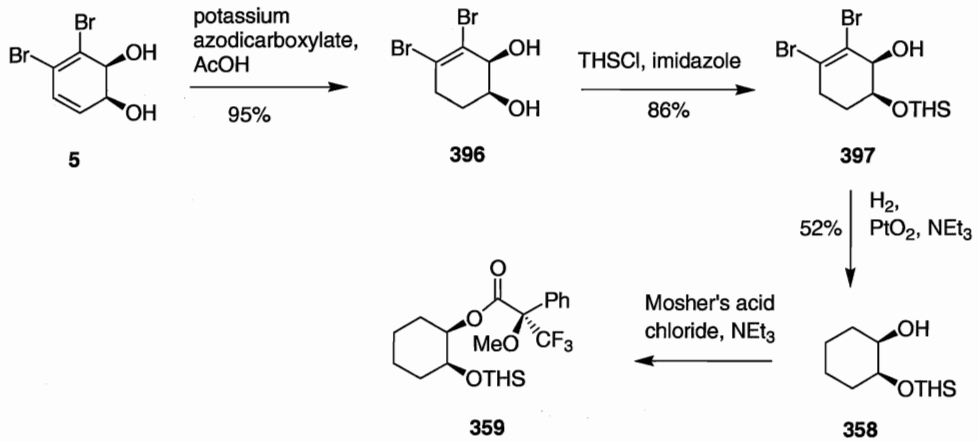
Figure 29. Symmetry of di-bromobenzenes and possible modes of oxidation.

The *o*-dibromo isomer **4** was oxidized by *E. coli* JM 109 (pDTG601) in a 15-L fermentor to give diene diol **5** in 4.1 g/L. Following a literature precedent, compound **5** was protected as its acetonide **394** and the more electron-rich olefin subjected to dihydroxylation to afford tetrol **318**. Removal of the both bromine atoms was accomplished smoothly using tri-*n*-butyl tin hydride to give the known compound **395**. According to a literature prodecure, the acetonide functionality was removed using 3% conc HCl in MeOH to give the natural product (-)-conduritol E in 81% yield. The optical purity of (-)-conduritol E **6** was compared to a literature value[163] and found to be within 3% error, Scheme 47.



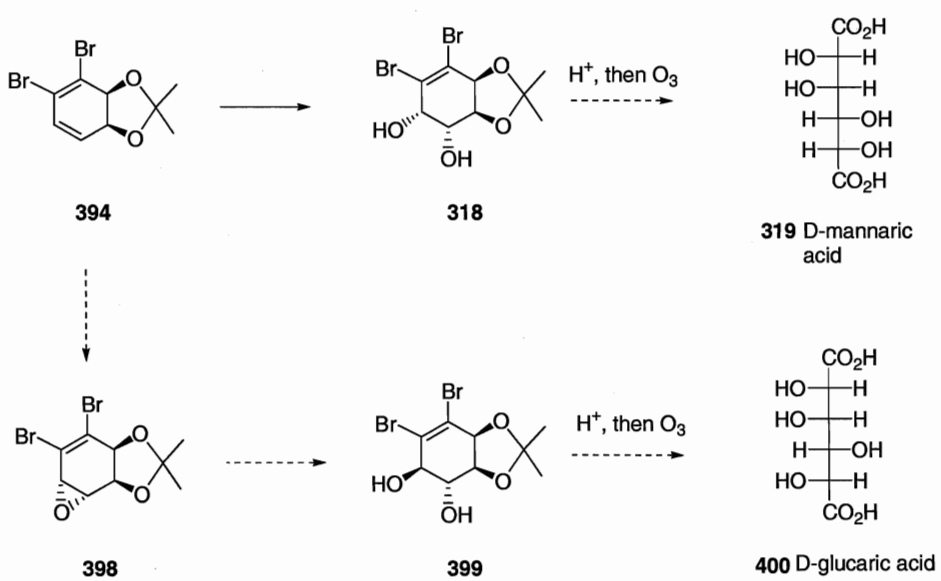
Scheme 47. Stereochemical correlation by conversion to (-)-conduritol E.

The absolute configuration of **5** was established by its conversion to conduritol E, as shown in Scheme 47, and its enantiomeric excess was conveniently determined by ^{19}F-NMR evaluation of the Mosher ester derived from mono-protected diol **360**, Scheme 48. The Mosher ester **361** was previously prepared from homochiral and racemic alcohols **360** in connection with our studies on the oxidation of bromothioanisoles. Analysis of the crude ^{19}F-NMR spectrum indicated the prescence of a single diastereomer, corresponding to an enantioselectivity of greater than 95% in the enzymatic oxidation of *o*-dibromobenzene.



Scheme 48. Determination of *ee* for metabolite **5**.

D-mannaric acid would easily be accessed from enantiomerically pure diol **318** by ozonolysis according to established procedures for the conversion of vinyl bromides to this type into hexoses.[31] The provision of isomeric sugars D-glucaric acid and D-altaric acid is also possible, as all four diastereoisomers at C-4 and C-5 are accessible by directed hydroxylation or epoxidation procedures. Diol **118** would appear to be suitable for synthesis of such acids.



Scheme 49. Programmed approach to sugars from halo-dienes.

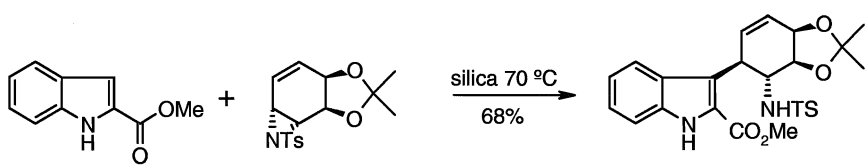
This type of programmed approach has been extended to the synthesis of inositols,[41] aminoconduritols,[57] and aza-sugars.[164] In this manner, diastereomeric analogues can be generated by either osmylation, or alternatively, epoxidation followed by nucleophilic opening of the epoxide in trans-diaxial fashion. Apart from the biological properties that aminoconduritols possess,[165] they are shown to be important builing blocks in a variety of natural products. Conduritols and aminoconduritols can be easily accessed through the intermediacy of their epoxide and aziridine precursors, respectively. Our reliance on epoxide and aziridine precursors derived from homochiral dienediols, therefore, prompted us to investigate new methods for selective opening of these intermediates which complemented our program in green chemistry.

III-4 Nucleophilic Opening of Strained Heterocycles Facilitated by Silica Gel

In connection with our interest in the generation of analogues of the powerful anti-tumor agent pancratistatin, we set out to synthesize such a derivative in which the aromatic nucleus was replaced by indole. We imagined that nucleophilic attack of a 2-substituted indole onto a vinyl aziridine would occur at C-3. Aziridines, however, are known to be more resistant to opening than their epoxide analogues,[166] and often require Lewis or protic acid catalysis in order to effect opening. Although a single report from the Yadaf group suggests that indoles readily undergo nucleophilic attack at C-3 under $InCl_3$ catalysis,[167] all attempts to carry out this transformation in our hands led to decomposition of the indole nucleus, with only trace amounts of the product arising from nucleophilic opening by C-3 of indole. Under strongly acidic conditions indoles are

known to dimerize, forming indigo or indirubin.[168] A notable exception to the incompatibility is Wenkert and Hudlicky's use of 10% aq HOAc as a mild protic acid in the synthesis of aspidosperma alkaloids from indole nuclei.

Our investigations into the use of silica gel as a mild acid catalyst stem from the incompatibility of indoles with many protic and Lewis acids. We envisioned that a β-carboline-1-one analogue of pancratistatin may arise from nucleophilic opening of a vinyl aziridine at the C-3 position of indole. Gratifyingly, Dr. Uwe Rinner discovered that the nucleophilic reaciton of indole derivatives with the requisite vinyl aziridine is facilitated on solid silica surface at 70 °C in the absence of solvent.



401 402 403

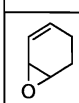
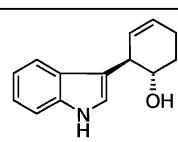
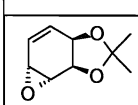
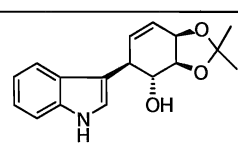
Scheme 50.

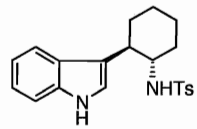
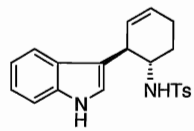
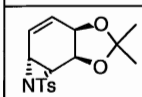
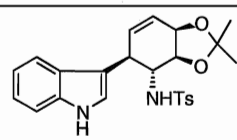
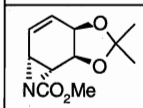
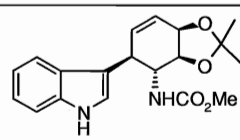
Moreover, indole-2-methyl ester, which may be considered deactivated toward attack by C-3 owing to resonance through the ester functionality, was found to exhibit superior reactivity relative to indole.

Vinyl epoxides **13** and **14** were synthesized according to the methods of Crandall[169] and Hudlicky,[27] respectively. Aziridines **402**,[44] **408**,[170] **410**,[171] and and were prepared as described in the published procedures. A general procedure was developed for the activation of silica gel, which required washing with THF, ether, and finally pentane. The silica was further activated by drying under high vacuum (ca 1 mm Hg) for a period of 12-24 h. The electrophile (1 equiv) and nucleophile (3 equiv) were suspended

in a minimal amount of methylene chloride and poured over activated silica gel. The methylene chloride was removed under reduced pressure and the silica gel containing the adsorbed reactants heated under argon atmosphere at 70 °C until consumption of the starting material was observed by TLC control. Following the precedent of the Yadaf group, who reported success using 10% $InCl_3$ in CH_2Cl_2, we originally hoped that silica gel catalysis in conjunction with a Lewis acid such as $InCl_3$ would promote the ring opening at or slightly above rt. Several hybrid silica/ acid catalytic systems were investigated, but none proved superior to solid silica gel at elevated temperature. Reactions of Lewis acid doped silica gel were difficult to purify owing to the tendency for these reactions to produce a variety of degradation products. The reactivity of an alternative $InCl_3$/silica surface (entry **d** in Table 7) was examined by pre-treating silica gel with 10% aq. $InCl_3$ prior to the standard activation protocol and the yield found to be equal to that for 5% $InCl_3$-doped silica surface reactions in the case of epoxide **406**. The results of the un-optimized ring-opening reactions promoted by silica gel are summarized in Tables 7 and 8.

Table 7. Reaction of Epoxides and Aziridines with Indole on Silica and in Solution.

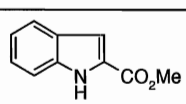
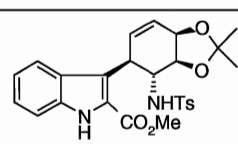
Electrophile	Condensation product	Yield*
 **404**	 **405**	**a) 32%** b) 22% c) 51%
 **406**	 **407**	**a) 51%** b) 8% c) 17% d) 17%

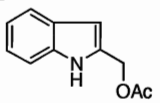
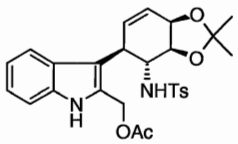
 **408**	 **409**	**a) 38%** b) <5% c) 26%
 **410**	 **411**	**a) 76%** b) 25% c) 66%
 **402**	 **403**	**a) 48%** b) 8% c) 31% d) 70%; rt, tlc plate
 **413**	 **414**	**a) 29%** b) not determined c) not determined

*Yields are isolated.

a) silica gel surface at 70 °C
b) 0.1 eq. $InCl_3$ in CH_2Cl_2
c) $InCl_3$-doped silica at 70 °C
d) 10 % aq. $InCl_3$-treated silica at 70 °C

Table 8. Reaction of 2-substituted Indoles with Aziridine 402.

Indole nucleophile	Condensation product	Yield*
 **401**	 **403**	**a) 68%** b) NR c) NR

 **415**	 **416**	**a) 24%** b) NR c) not determined

*Yields are isolated.

a) silica gel surface at 70 °C
b) 0.1 eq. $InCl_3$ in CH_2Cl_2
c) $InCl_3$-doped silica at 70 °C

The reactions of *N*-*t*-butoxycarbonyl and *N*-carbomethoxy-protected aziridines with indole was briefly examined. The Boc-protecting group was found to be labile under optimized reaction conditions (70 °C) and this substrate was un-reactive at rt. *N*-carbomethoxyaziridine was un-reactive at rt and the reaction not investigated at elevated temperatures.

To the best of our knowledge, not a single general report describing the reactions of azirdines and epoxides with indole nucleophiles on silica surface was known at the time that this work was carried out. Satisfied that we had developed a general protocol for the nucleophilic opening of strained heterocycles by acid-labile compounds, Dr. Rinner and Prof. Hudlicky turned their attention to completion of the target molecule. A retrosynthetic disconnection to the key precursors in shown below.

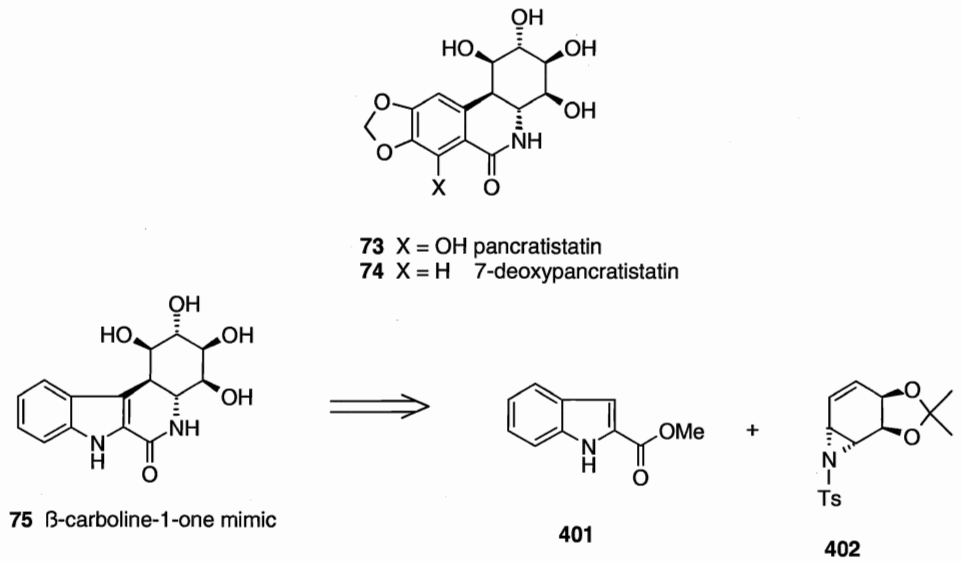
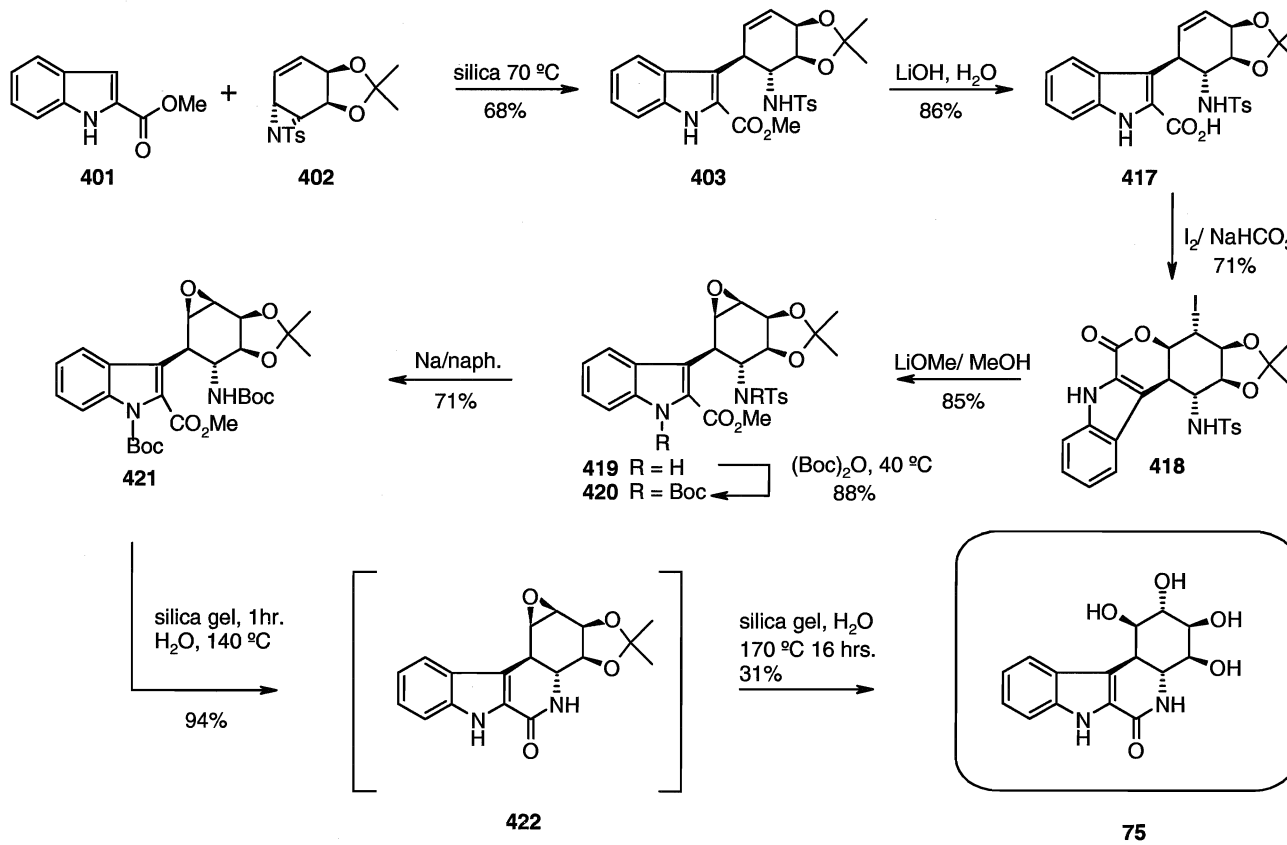


Figure 30. Retrosynthetic analysis of β-carboline-1-one mimic of pancratistatin.

With multigram quantities of intermediate **403**, the synthesis of the β-carboline-1-one mimic of pancratistatin was completed according to Scheme 51.[172] Silica gel plays a critical role in several late-stage steps of the synthesis. Heating bis-Boc derivative **421** on silica surface allowed a thermal deprotection of the carbamates, and subsequent closure of the resulting amine to give the amide **422**. Further heating of **422** on silica surface installed the remaining hydroxyl functionality by acid-catalyzed epoxide opening, and finally, deprotection of the acetonide protecting group was accomplished to provide the target molecule **75**.



Scheme 51. Completion of β-carboline-1-one mimic of pancratistatin.

A detailed NMR study was initiated in cooperation with Dr. Ion Ghiviriga (The University of Florida) to assess whether the opening of vinyl epoxides proceeded in a S_N2' fashion at the distal olefinic center (producing **407-alt**) or in the expected S_N2 manner to yield **407**. Analysis of long-range couplings in the HMBC NMR spectrum established that carbon 40.8 ppm is connected to the indole ring. Dr. Ghiviriga writes,[173] "One can easily make three arguments for assignment of structure **407**, as opposed to **407-alt**: *i*) the proton at 3.89 ppm displays two large couplings, 9.0 and 10.0 Hz, therefore it is axial and its vicinal protons at 3.54 and 4.22 ppm are also axial, which would imply a *trans* relationship of the protons in the acetonide moiety in **407-alt**. *ii)* the chemical shifts of the protons at 4.22 and 4.76 ppm and their coupling constant of 6.6 Hz

are expected for the acetonide moiety represented in **407**. *iii)* the proton at 1.45 ppm displays an nOe with the protons at 4.76, but not with that at 3.89 ppm."

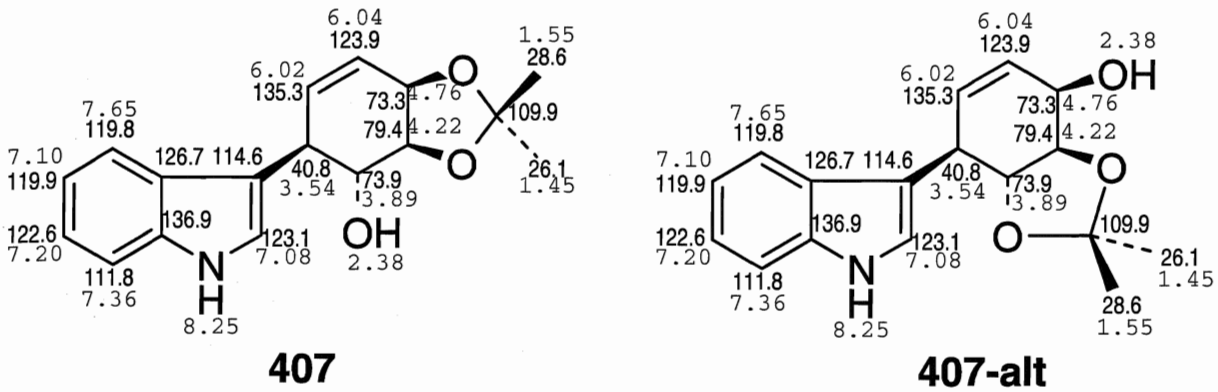
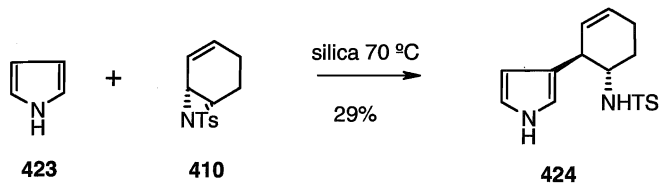


Figure 8. NMR assignment of compound **407.**

The present study provides an excellent example of the generality and mildness of silica gel as a Lewis-acid catalyst. Indole nuclei, which are notoriously unstable toward even mildly acidic conditions, are readily reacted with a variety of strained heterocycles on the surface of silica gel. The reactions facilitated by silica gel provide a mild alternative to Lewis- or protic acid catalysis. Such reactions could provide an entry to a variety of indole-based natural products containing oxygen or nitrogen functionalities. The reactivity of other aromatic nucleophiles, however, is largely unexplored. A single experiment in which pyrrole was reacted with vinyl aziridine **410** was examined, giving the coupled product tentatively assigned as **424**, Scheme 52. Future work will include a series of heteroaromatic nuclei, such as furans, benzofurans, thiophenes, etc. which will further demonstrate the generality of this methodology.



Scheme 52. Reaction of pyrrole and vinyl aziridine **410**.

III-5 Oxidations of Aromatics Containing Remote Chiral Centers. Studies on Aromatic Cyclopropanes.

The products arising from oxidation of aromatic compounds containing racemic or chiral centers account for less than 10 percent of all the known diene diol metabolites. Substrates in which the chiral center lies proximal to the site of oxidation on the ring present an opportunity for resolution of pro-chiral centers by the enzyme. Studies on the oxidation of 1-phenethyl alcohol using *Pseudomonas putida* expressing toluene dioxygenase by Ribbons resulted in a slight preference for the formation of the (S)-enantiomer in the diastereomeric oxidation products, Figure 32.

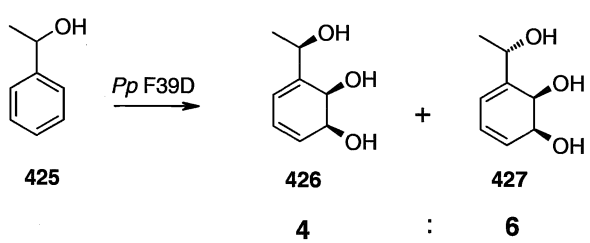


Figure 32.

The work was later repeated using *E. coli* which over-express the enzyme toluene dioxygenase and surprisingly, they found that oxidation with this organism resulted in an equal distribution of diasteromeric diols. A collaborative effort between the Hudlicky and Ribbons groups undertook a general study of substrate specificity and product

distribution in which a variety of substrates having chiral or racemic benzylic centers were subjected to oxidation with both *E. coli* JM 109 and *Pseudomonas putida* F39D.

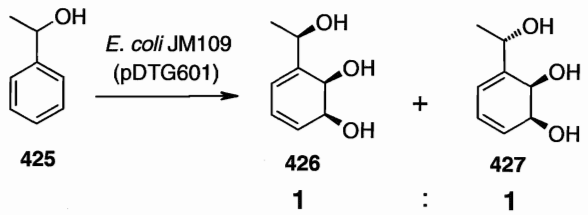


Figure 33.

With the exception of 1-phenethyl alcohol **425**, which was consistently found to give a preference for the (S)-isomer by oxidation with *Pseudomonas putita*, all substrates were oxidized to give equal mixtures of diasteremeric products. We became interested in the oxidation of substituted cyclopropanes because they represent a series of substrates in which a racemic center lies proximal to the site of oxidation. Such a series would allow us to investigate the possibility of performing a resolution of chiral centers through enzymatic oxidation.

Cyclopropylbenzene was initially investigated in connection with a study focusing on elucidation of the mechanism of oxidation.[134] We were encouraged by the high yield of the diol from oxidation and the possibilities for further fuctionalization of the metabolites as shown in Figure 34.

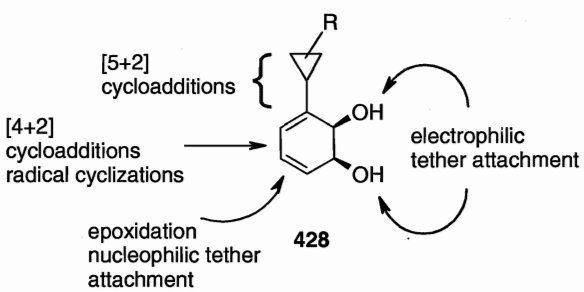
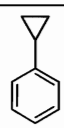
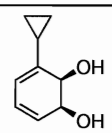
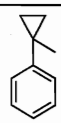
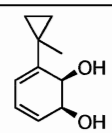
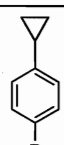
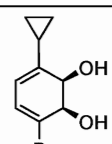
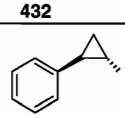
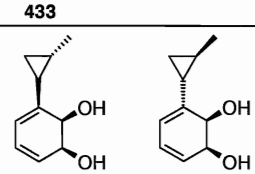
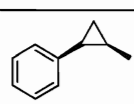
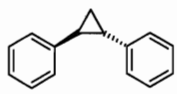
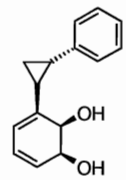
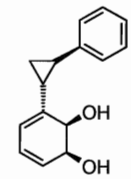
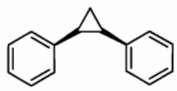
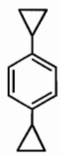


Figure 34. Reactive options of homochiral dienylcyclopropanes obtained from enzymatic oxidation of the corresponding arenes.

We synthesized a series of cyclopropylbenzenes, which were subjected to oxidation with *E. coli* JM 109 (pDTG601). The products of fermentation were extracted from the fermentation broth into ethyl acetate, purified, and fully characterized. The absolute configuration of each metabolite was proven unambiguously by chemical match with synthetic material derived from diol **72**, whose absolute stereochemistry has been firmly established,[7] except in the case of metabolite **434**, whose match was made from known diol **452**.[174]

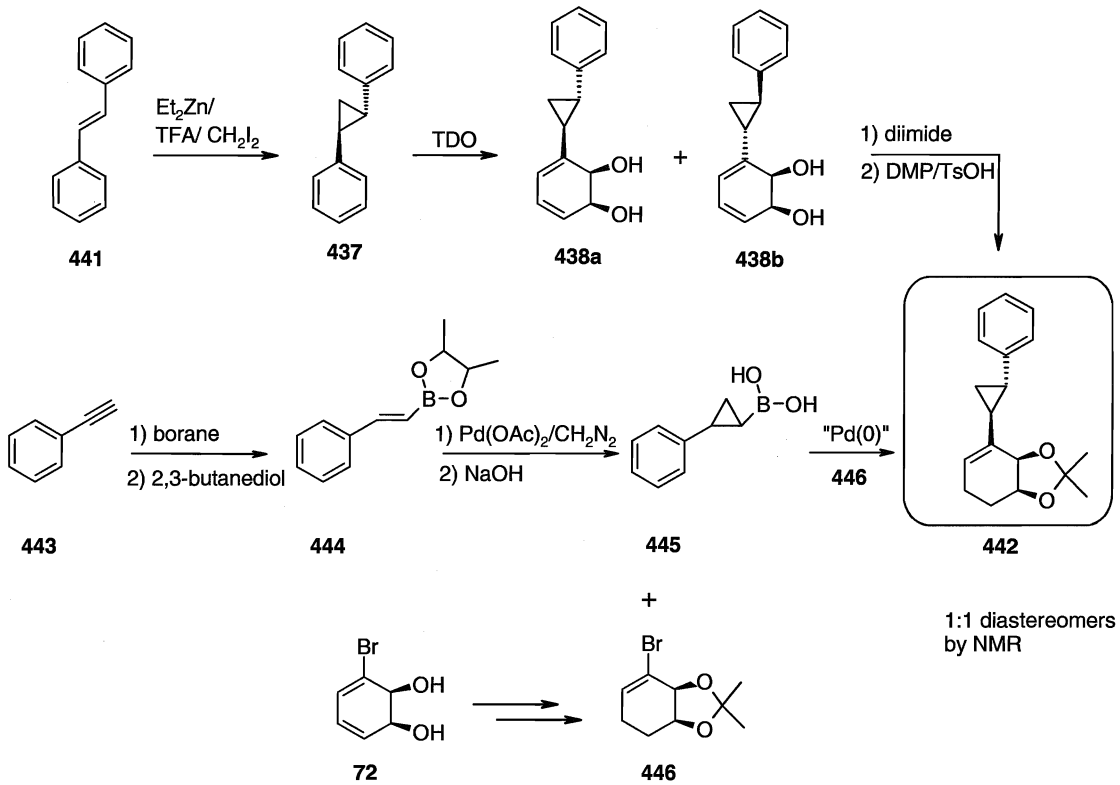
Table 9. Results of Enzymatic Oxidation of Cyclopropylarenes by *E. coli* JM 109 (pDTG601)

Entry	Substrate	Product	Yield (mg/L)
1[a]	 **429**	 **428**	2500
2	 **430**	 **431**	56
3	 **432**	 **433**	32
4	 **434**	 **435a (1:1) 435b**	90
5[b]	 **436**	---	---

6	 437	  438a (1:1) 438b	140
7^b	 439	---	---
8^c	 440	---	---

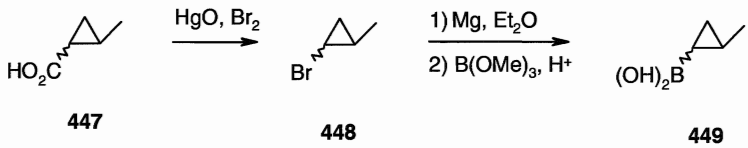
[a] Biotransformation of substrate **429** was performed in a 15-L fermentor.
[b] ^{1}H NMR spectra of the crude residue from biooxidation of *cis* configured cyclopropanes revealed the presence of only trace amounts of the corresponding diene-diols.
[c] Only starting material was recovered.

Oxidation of cyclopropylstilbene **437** gave diene-diols **438**, which were reduced with potassium azodicarboxylate/acetic acid. The diol was protected as its acetonide to afford **445**, Scheme 52. Analysis of ^{1}H and ^{13}C NMR spectral data for compound **445** revealed an approximate 1:1 ratio of diastereoisomers. The absolute configuration was proven by conversion of phenylacetylene **443** to the corresponding cyclopropylboronic acid **445**, which was subjected to a Suzuki coupling protocol with vinyl bromide **446**, prepared from homochiral bromodienediol **72**. Spectral data and optical rotation of **442**, synthesized from compound **72**, provided the proof of absolute configuration of the trans isomer **438**.



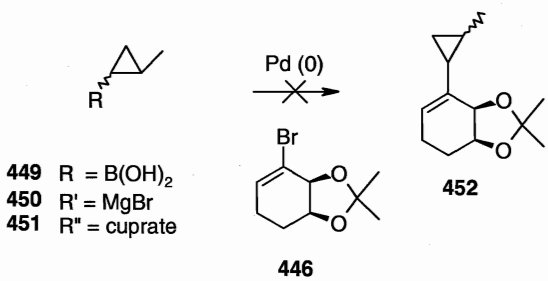
Scheme 52.

By analogy to the sequence shown in Scheme 52, we imagined that the configuration of compound **435** could be proved by a Suzuki coupling reaction in which racemic methylcyclopropyl boronic acid would undergo palladium catalyzed coupling with vinyl bromide **446**. To this end, the cyclopropylbromide **448** was prepared from acid **447** by a Hunsdiecker reaction in the presence of mercuric acetate and bromine, Scheme 53. The bromide was converted to its Grignard reagent, which was directly quenched with freshly distilled trimethyl borate and acidified to give the corresponding boronic acid **449**.



Scheme 53. Synthesis of Suzuki coupling precursor **449**.

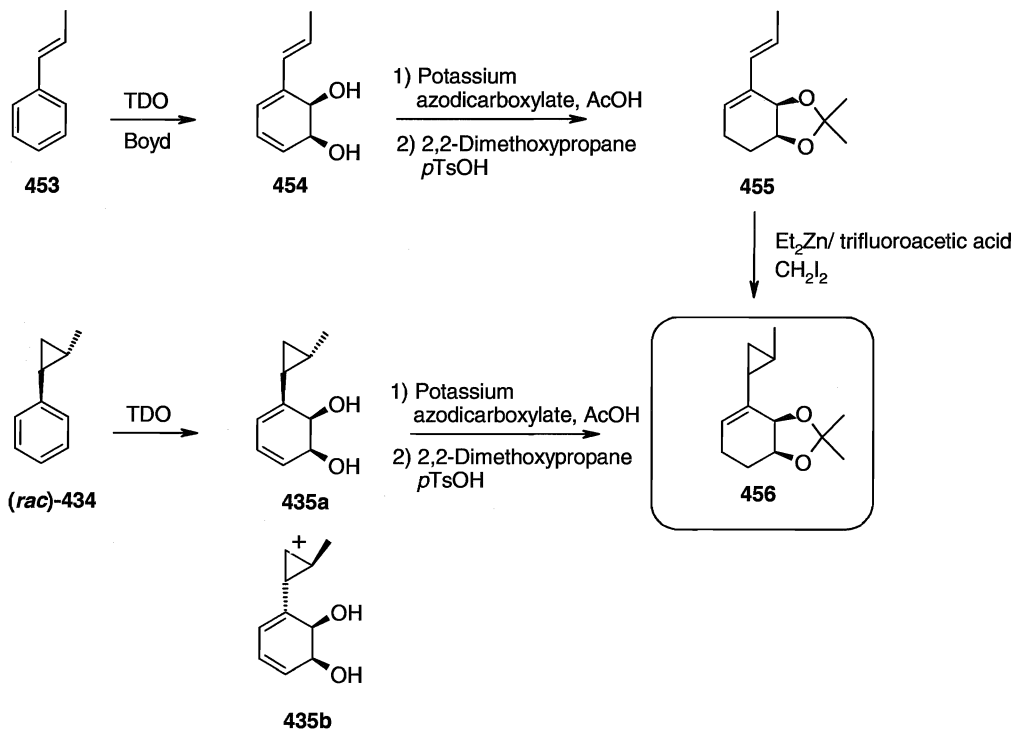
A variety of unsuccessful conditions were investigated to effect coupling of vinyl bromide **446** to the boronic acid **449** by a Suzuki protocol. Alternative coupling procedures involving the Grignard or cuprate derivative of cyclopropyl with vinyl bromide **446** met with limited success; in most cases, the vinyl bromide was re-isolated. Relatively few reports of successful Pd-reactions involving cyclopropanes are known, probably owing to the ease of opening and polymerization of cyclopropanes in the presence of palladium.



Scheme 54. Attempts to introduce cyclopropane by coupling reactions.

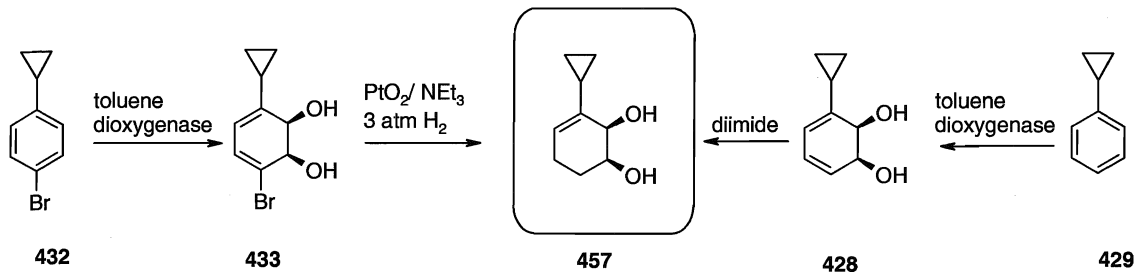
Proof of absolute configuration of compound **435** ultimately relied on correlation with a known diol, **454**, which results from fermentation of *trans*-β-methylstyrene **453**, and was initially reported by Boyd and co-workers.[174] Fermentation of *trans*-β-methylstyrene gave the corresponding chiral trienediol **454**, which was reduced with diimide to its more stable diene. The diol functionality was protected as its acetonide **455** and the less-substituted olefin converted to its corresponding cyclopropane **456**, formed as a single

diastereoisomer whose sign of optical rotation matched that of compound **435** prepared by fermentation of cyclopropyl benzene **434**.



Scheme 55.

The configuration of metabolite **433** was determined by conversion to vinylcyclopropane **457** by hydrogenation with Adams' catalyst in triethylamine. The configuration of diol **457** was correlated to diol **428**, as shown in Scheme 56. The absolute configuration of diol **428** had been previously matched to diol **72**.[134] While oxidation of cyclopropylbenzene proceeds to give essentially enantiomerically pure dienediol, enzymatic oxidation of *p*-bromocyclopropylbenzene provides material of only 27% optical purity, bearing the absolute configuration shown in Scheme 56.



432 **433** **457** **428** **429**

27% optical purity

Scheme 56.

Chiral dioxygenase metabolites bearing a cyclopropyl unit represent a new class of arene diene diols which may find application in asymmetric synthesis. Two general types of these substrates were investigated with respect to their tendency to undergo oxidation and respective stereochemical outcome: (1) mono-substituted aromatic cyclopropanes bearing a racemic benzylic center; (2) di-substituted aromatic compounds bearing an unsubstituted cyclopropane. Mono-substituted compounds having *cis*-stereochemistry were not found to be accepted as substrates for the enzyme and starting material was recovered from these fermentations, whereas their *trans*-substituted counterparts were found to be good substrates for the enzyme and gave mixtures of diastereomers. In accordance with Boyd's explanation for rationalization for stereochemistry in mono-substituted systems, we propose that it is the larger of the two groups, i.e., the one which bears asymmetry which must lie outside the active site during oxidation and therefore is unable to be recognized by the enzyme, Figure 35. Such a hypothesis would support our finding that no diastereoselectivity was observed in the oxidation of racemic cyclopropanes.

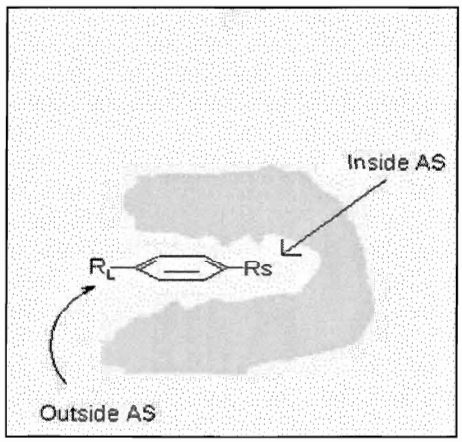


Figure 35. Cartoon representation of substrate in active site of enzyme.

III-6 Approaches to the Chemical Synthesis of Morphine

III-6.1 Diels-Alder Approach Using Thiophene as a Latent Diene

In the last several years, Diels-Alder reactions involving heteroaromatic systems have witnessed broad application. Padwa has utilized furan cycloadditions as an entry to the *Amaryllicidacae* and vindoline families of natural products.[175] Similar heteroaromatic cycloadditions have been employed in the synthesis of various indole-containing natural products by Boger.[176] An extention to this cycloaddition chemistry involves the use of thiophene-1,1-dioxide or thiophene-1-oxide as a latent diene synthetic equivalent.[177] By occupation of the lone pairs in bond formation, the thiophene is rendered far less aromatic, and therefore less stable, and the diene portion of the molecule has proven to be susceptible to Diels-Alder chemistry. Unlike its furan counterpart, the sulfone or sulfoxide functionality present in the Diels-Alder adduct can be excised by thermal

cheleotropic extrusion on heating. The application of such chemistry in the construction of natural products has not yet been realized and there is still much to learn regarding the scope and mechanism of these reactions.

Our proposed synthesis of thebaine would take advantage of the pseudo-C_2 symmetry present in the target. Indeed, a strategic intermediate is the symmetrical alkyne **12**. The key step, which would simultaneously construct the complete pentacycle, relies on a tandem enzymatic sulfoxidation-Diels-Alder sequence.

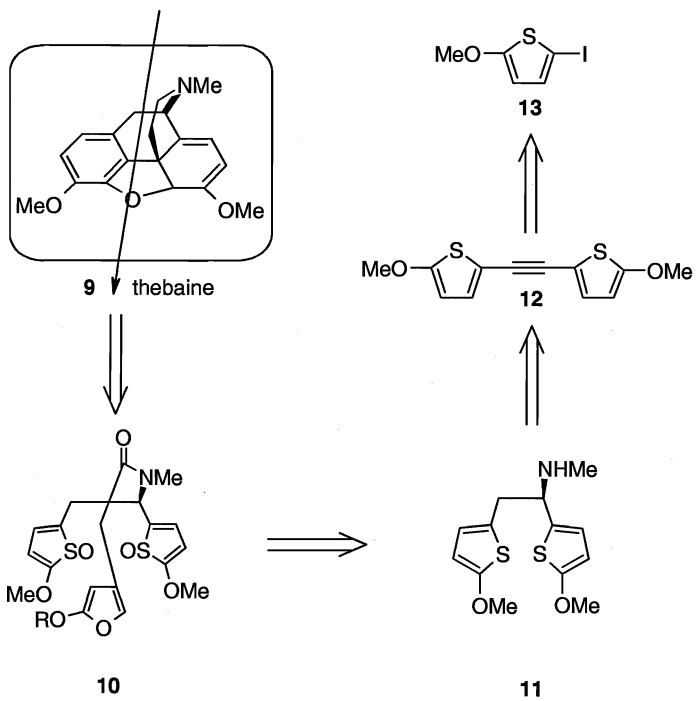


Figure 36. Retrosynthetic analysis of thebaine.

In connection with our interest in the oxidation of aromatic compounds using bacterial enzymes, the key strategy in our approach to thebaine would rely on a tandem sulfoxidation/ intramolecular Diels-Alder reaction to establish the C-13 quaternary center in the natural product. The oxidation at sulfur could be mediated enzymatically, or by

standard chemical oxidants. Failing the thiophene-oxide cycloaddition, an alternative strategy for the construction of the pentacycle could be established by an analogous intramolecular Diels-Alder with furan (IMDAF) reaction.

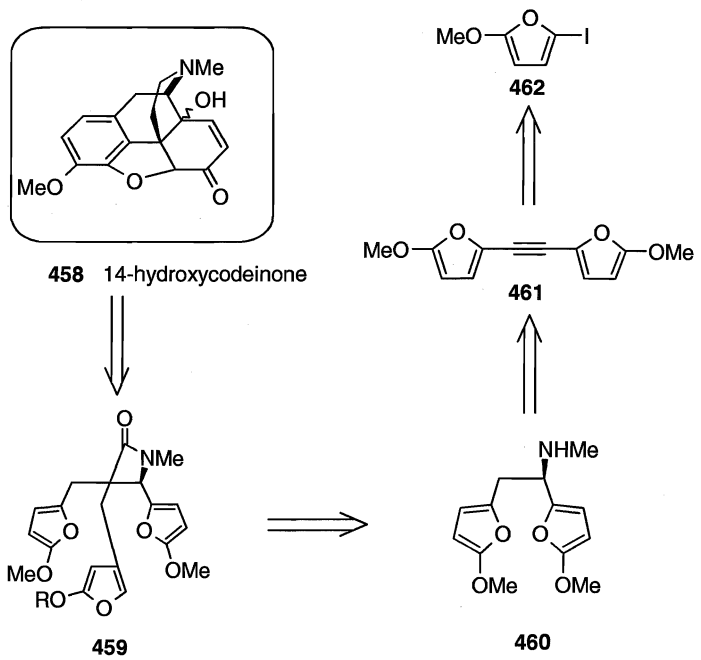
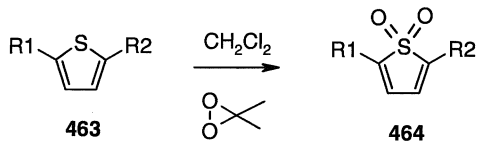


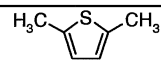
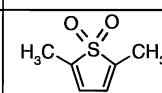
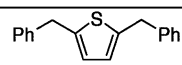
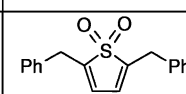
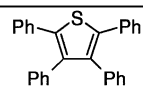
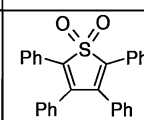
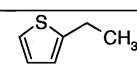
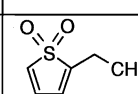
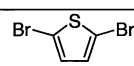
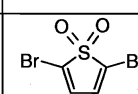
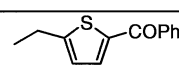
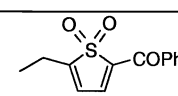
Figure 37. An alternative retrosynthetic analysis of morphinan 14-hydroxycodeinone.

Several examples describing the chemical oxidation of the divalent sulfur atom in thiophenes have been reported.[178] The oxidation of sulfur to its thiophene-1-oxide renders the sulfur more susceptible to oxidation than its precursor. Thiophene-1-oxides are highly-reactive, transient species which undergo dimerization reactions by Diels-Alder cyclization in the absence of an external olefinic or alkynyl cycloaddition partner. Sterically-congested thiophenes are readily oxidized to their corresponding dioxides, and several examples of isolable thiophene-1,1-dioxides have been reported.[179]



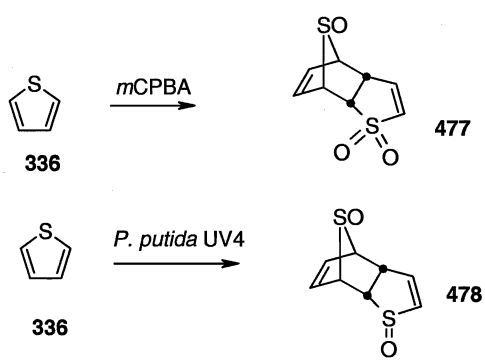
Scheme 57. Oxidation of divalent sulfur in thiophenes.

Table 10. Synthesis of thiophene-1,1-dioxides by dioxirane oxidation.[180]

Entry	Thiophene	Thiophene-1,1-dioxide	Yield (%)
1	 465	 466	93
2	 467	 468	93
3	 469	 470	99
4	 471	 472	0
5	 473	 474	27
6	 475	 476	73

Entry 4 of Table 10 is noteworthy; attempted oxidation of 2-ethylthiophene did not produce the corresponding dioxide. Although the authors did not offer an explanation for this lack of oxidation, van Tilborg reports[180] that oxidation of 2-methylthiophene with

*m*CPBA produces, apart from the expected dioxide (18.7% yield) at least 32 by products from oxidation (determined by analysis of the crude reaction mixture by HPLC). The decomposition of 2-methyl-subsitituted thiophenes may be attributed, in part, to its tendency to undergo oxidation at the methyl group, eventually leading to ring opening processes. Thiophene itself is too unstable to be isolated as its 1,1-dioxide, but the dimerized products have been well characterized. Boyd has reported the enzymatic oxidation of thiophene and several derivatives by enzymatic oxidation with the mutant strain *Pseudomonas putida* UV4, a strain which over-expresses the enzyme toluene dioxygenase.[140] Once oxidized, these unstable thiophenes undergo Diel-Alder dimerization. Interestingly, the enzymatic pathway is the only example of selective thiophene oxidation to its corresponding sulfoxide, without over-oxidation to the sulfone.



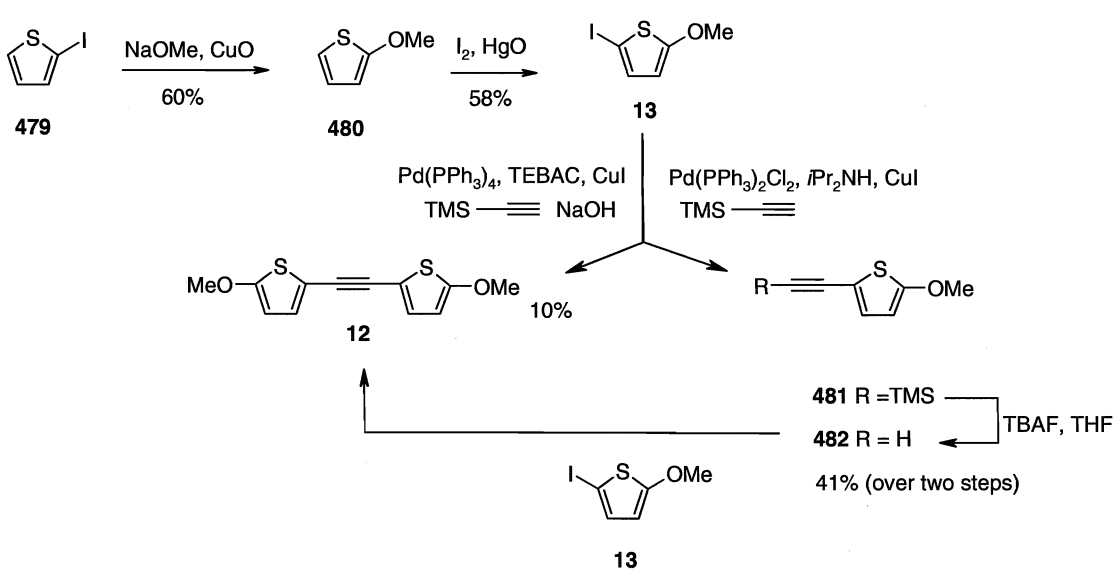
Scheme 58. Divergent modes oxidation of thiophene by chemical and enzymatic means.

In a 1976 Acta Chemica Scandinavica publication, Kurt Torssell wrote:

> "It therefore seemed reasonable to anticipate the formation of Diel-Alder adducts when the sulfoxide was generated in presence of suitable enes."

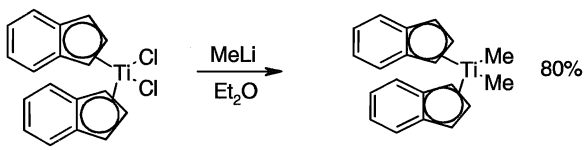
With Professor Torssell's words in mind, we embarked on a synthesis of symmetrical alkyne **12.** We hoped to install the methylamino functionality through a Ti-catalyzed hydroamination reaction. Acylation of the amino group with the appropriate furanyl

tether would set the stage to carry out the tandem oxidation/Diels-Alder reaction. The synthesis began with commercially available 2-iodothiophene, which was converted to its 2-methoxy derivative by treatment with sodium methoxide and cupric oxide in refluxing methanol, according to the procedure of Sice'.[181] 2-Methoxythiophene is readily converted to its 5-lithio species by treatment with *n*-butyllithium, and the resulting anion quenched with iodine. Installation of iodine at the 5-position provided a functional handle for Sonagashira chemistry, and 2-iodo-5-methoxythiophene **13** was subjected to a variety of standard conditions in order to effect Pd-catalyzed cross coupling to give alkyne **12**. Compound **12** could be prepared in a single step,[182] albeit in low yield. Additionally, the procedure was not amenable to scale-up and the yields were capricious. Although the 2-bromo-5-methoxythiophenecould also be readily prepared, the bromide proved resistant to coupling. A less direct route was realized by stepwise introduction of the alkynyl portion, removal of the silyl protecting group, and exposure of this material to another coupling reaction with 2-iodo-5-methoxythiophene.[183]



Scheme 59. Preparation of hydroamination precursor **12**.

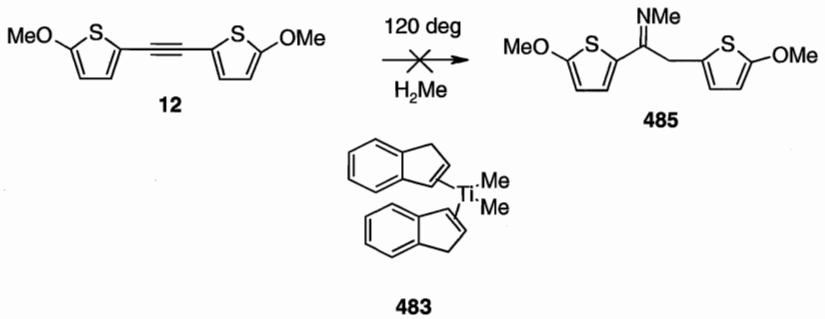
With acetylene **12** in hand, the Doye's Ti-based hydroamination catalyst was prepared from bis-indenyl titanium dichloride by treatment with 2 equiv of methyllithium in diethylether.[184]



483 **484**

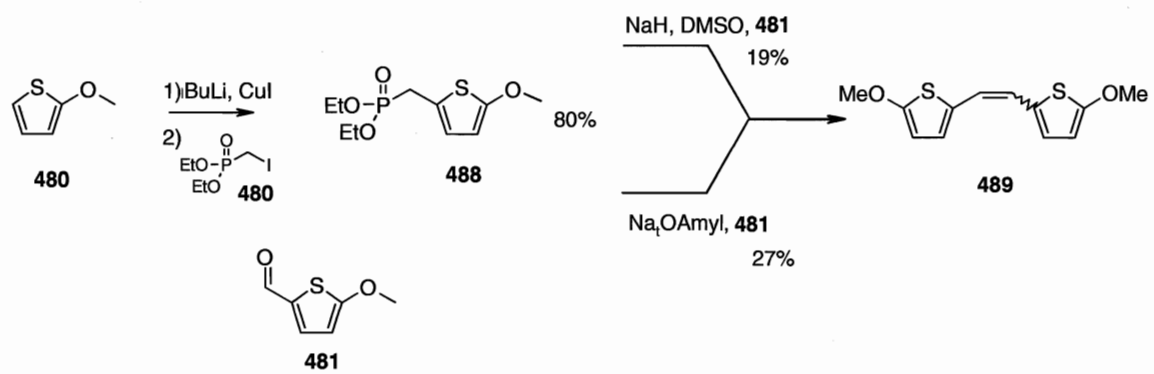
Scheme 60. Preparation of Doye's hydroamination catalyst.

At that time, there were no reports which described the application of hydroamination to small molecule amines and several sets of conditions were attempted to introduce the methylamine functionality. Initially, a toluene solution of alkyne **12** was introduced to a Teflon-sealed Schlenk tube, degassed under a positive pressure of nitrogen, a THF solution of methylamine was added, and the tube sealed and heated to 120 °C. After heating the reaction mixture for several days, the starting alkyne was returned unchanged. Professor Doye, who was at that time extending his hydroamination research to include methyl- and ethylamine, suggested[185] that we use employ gaseous methylamine and treat the crude product with sodium cyanoborohydride to reduce the resulting imine to its stable methylamine derivative. These modified conditions, again, resulted in recovery of the starting alkyne.



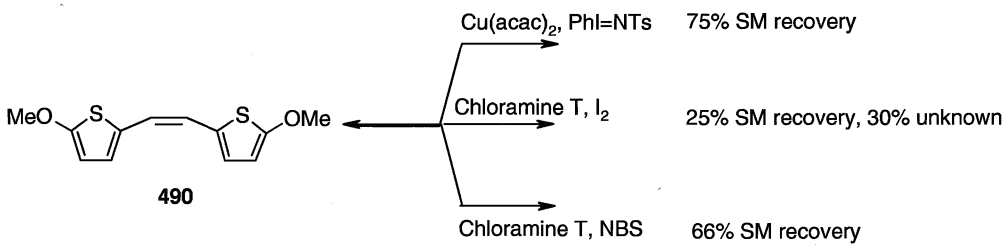
Scheme 61.

We decided to change our strategy synthesizing an olefinic thiophene dimer, such as **489**. Such a strategy would allow introduction of the requisite methylamine by reaction of methylamine with its epoxide derivative, or more directly, by conversion of the olefin to its aziridine, followed by treatment with a source of hydride.



Scheme 62.

In this manner, the olefin **489** was prepared in low yield by condensation of Horner-Wadsworth-Emmons derivative **488** with the aldehyde **481**. The *cis*-olefin was also prepared by hydrogenation with Lindlar catalyst, and several unsuccessful attempts were made to introduce an aziridine functionality. The approach was soon abandoned in favor of testing the key step in the form of a model substrate.



Scheme 63.

We decided to focus our attention on several model studies which would allow us to quickly assess the feasibility of the tandem oxidation/Diels-Alder sequence. Several generations of model system were synthesized; each model system increased progressively in complexity.

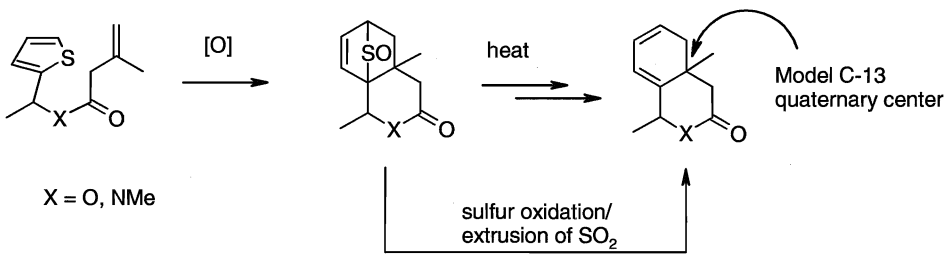
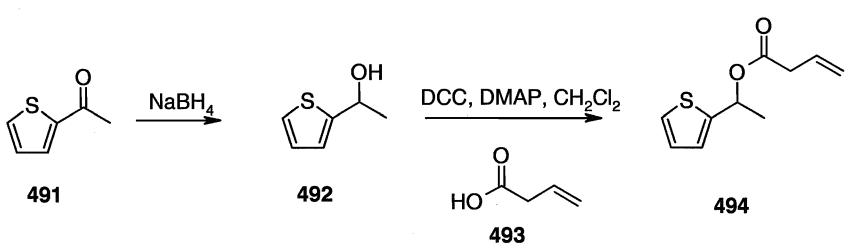


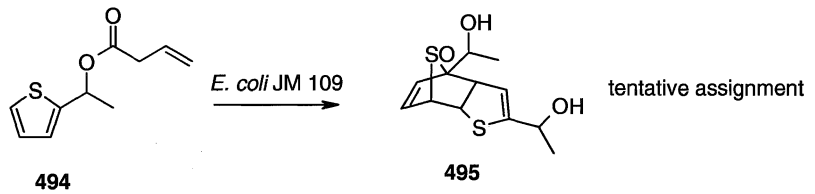
Figure 22. Model study for assessment of tandem oxidation/Diels-Alder sequence.

The first, and simplest, model was synthesized from commercially available 2-acetylthiophene **491** by borohydride reduction of the ketone to alcohol **492** and DCC coupling of the alcohol with vinyl acetic acid **493**.



Scheme 64.

The ester was screened for its tendency to undergo oxidation by *Escherichia coli* JM 109 pDTG061, a recombinant strain which over-produces the enzyme toluene dioxygenase. Oxidation of the simplest model **494** produced a small amount of a bicyclic compound, tentatively assigned as the mixture of diastereomers **495**.



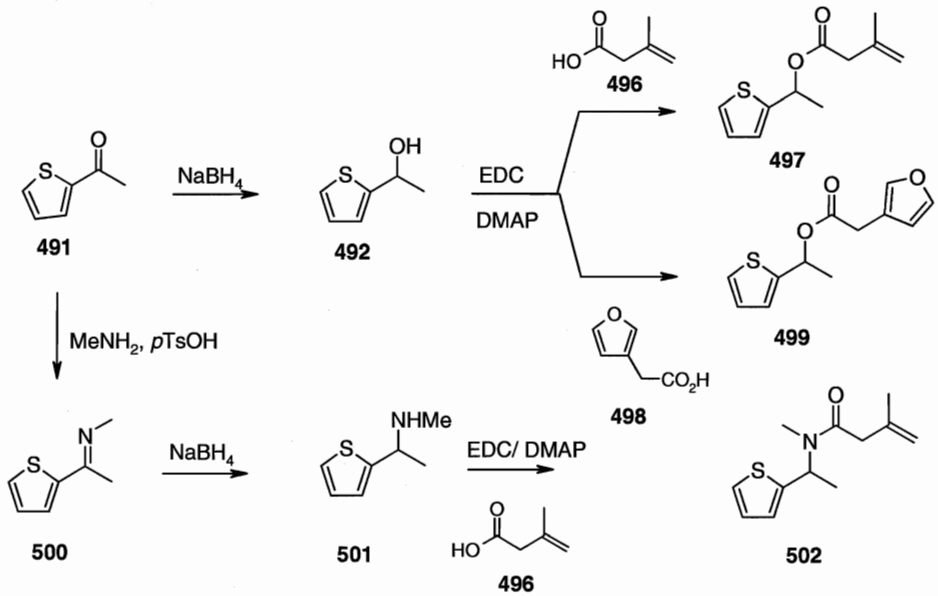
494 **495**

(5:1 mixture of isomers)

Scheme 65.

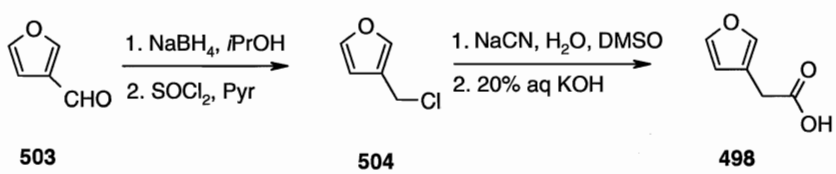
Compound **495** proved to be unstable and eluded attempts at rigorous purification. This may be attributed to its tendency to undergo air oxidation to its aromatic analogue. Analysis of the the ^{1}H NMR spectrum clearly shows a characteristic AB splitting pattern (in a 5:1 ratio) as one would expect to from bicyclic derivatives. IR spectroscopy reveals the absence of the ester functionality and the appearance of the hydroxyl functionality. All attempts to repeat this experiment gave the product of ester hydrolysis. We chose to reinvestigate the enzymatic oxidation of the model compounds which bear additional substitution on the olefinic side chain, a feature which would prevent re-aromatization.

2-Acetylthiophene was reduced with sodium borohydride, and the alcohol esterified with one of two acids having an appropriate olefinic tethers, Scheme 66. Similarly, the Schiff base prepared by condensation of methylamine with 2-acetylthiophene was reduced with sodium borohydride, and a similar activated ester coupling protocol was used for synthesis of the analogous amide. Acid **496** was prepared by a solid carbon dioxide quench of the Grignard reagent prepared from 2-methyl-3-bromopropene.



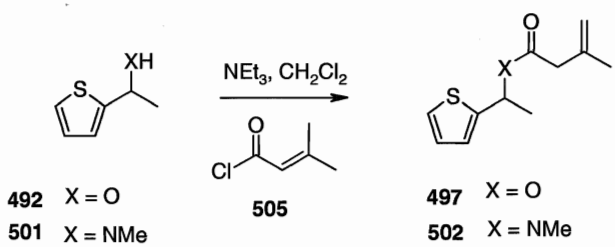
Scheme 66.

2-Furanyl acetic acid **498** was prepared in four steps from furan-3-carboxaldehyde according to a published procedure.[186]



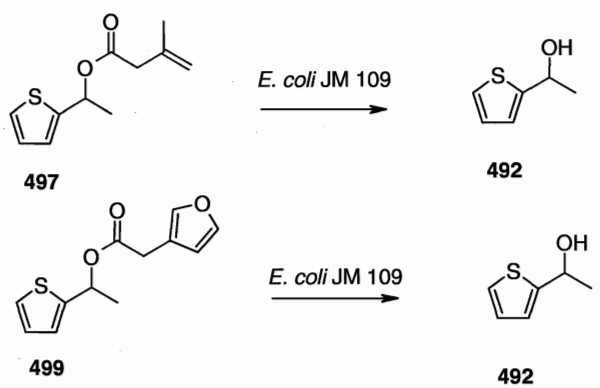
Scheme 67. Synthesis of 3-furanyl acetic acid.

A more direct route to the requisite esters and amides was developed by *in situ* formation of the ketene[187] derived from 2,2-dimethylacryllic acid chloride and trapping with either the alcohol or amine, respectively.



Scheme 68. Alternative route to deconjugated esters and amides.

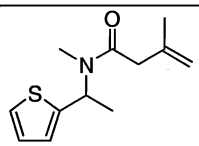
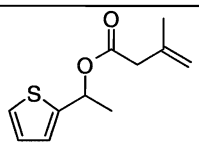
Esters **497** and **499** were subjected to enzymatic oxidation with *Escherichia coli* JM 109 pDTG061, Scheme 69. Both experiments resulted in nearly quantitative cleavage of the ester functionality, presumably by non-specific proteolytic enzymes, based on the fact that enzymatic reactions were carried out at neutral pH.



Scheme 69. Proteolytic cleavage of esters by *Escherichia coli* JM 109.

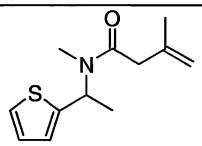
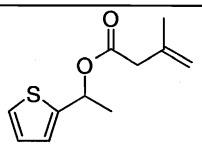
We turned our attention to oxidation of the analogous tethered amides, as the amide functionality is known to be more resistant toward enzyme-mediated cleavage. The amide was, indeed, stable to hydrolysis, but the amide was also resistant to enzymatic oxidation.

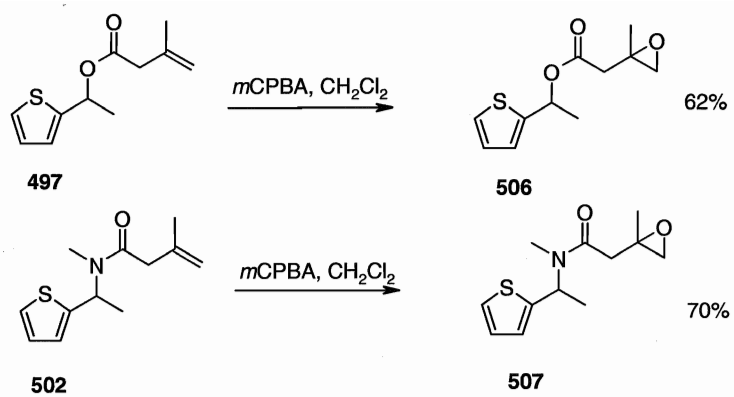
Table 11. Enzymatic Oxidation of Olefin-tethered Thiophene Amides and Esters.

	Conditions	Result
 502	JM 109 (pDTG601A)	Recovery of starting material
	JM 109 (pDTG141)	Recovery/isomerization of starting material
	Chloroperoxidase	Persistence of starting material by TLC
	Conditions	**Result**
 497	JM 109 (pDTG601A)	Recovery of hydrolysis product (10%)
	JM 109 (pDTG141)	Recovery of hydrolysis product

The difficulties encountered in enzymatic oxidations prompted us to investigate chemical oxidation of divalent sulfur. Owing to the aromatic nature of thiophene, the conditions reported for oxidation are more limited than those used for standard oxidation of divalent sulfur. By far the most common conditions reported for synthesis of thiophene sulfones is the treatment of thiophene derivatives with *m*CPBA in dichloromethane as reaction medium. In our hands, these conditions led to selective oxidation olefin rather than sulfur, Scheme 70.

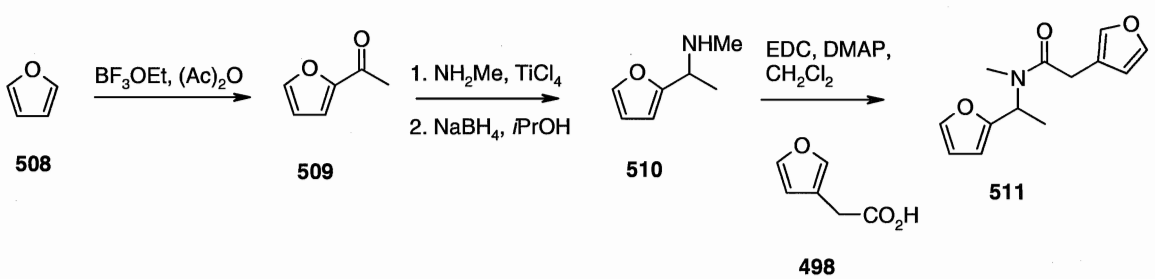
Table 12. Chemical Oxidation of Olefin-tethered Thiophene Esters and Amides.

	Conditions	**Result**
 **502**	$NaIO_4$, H_2O, MeOH, rt	Recovery of starting material
	$BF_3 \cdot OEt$, *m*CPBA syringe pump addition, -60 °C to rt	Decomposition of starting material
	*m*CPBA syringe pump addition, 0 °C	Epoxidation product- 50% conversion
	Oxone, acetone, $NaHCO_3$, rt	Persistence of starting material by TLC
	MnO_2, 37% HCl	Decomposition of starting material
	30% H_2O_2, MeOH, rt	Recovery of starting material-60%, trace of aromatic
	30% H_2O_2, ammonium molybdate, water/acetone	Persistence of starting material by TLC
	$RuCl_3 \cdot 3H_2O$, $NaIO_4$, H_2O, CCl_4, acetonitrile	Recovery of starting material + isomerization of olefin
	$NaBO_4$, AcOH, 50 °C	25% isomerization of olefin
	Conditions	**Result**
 **497**	$NaIO_4$, H_2O, MeOH, rt	Recovery of starting material
	*m*CPBA syringe pump addition, 0 °C	Epoxidation product- 62% conversion
	Oxone, acetone, $NaHCO_3$, rt	Persistence of starting material by TLC
	MnO_2, 37% HCl	Decomposition of starting material
	30% H_2O_2, MeOH, rt	Recovery of starting material
	30% H_2O_2, ammonium molybdate, water/acetone	Persistence of starting material by TLC
	$NaBO_4$, AcOH, 50 °C	25% isomerization of olefin
	10% $_{(aq)}$ bleach	Persistence of starting material by TLC



Scheme 70.

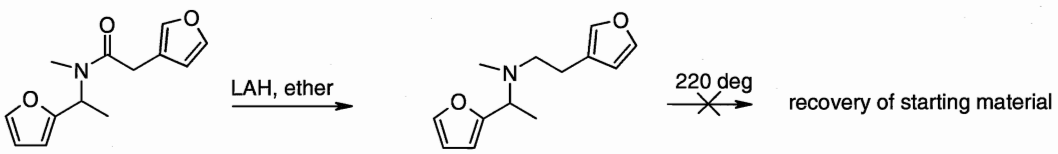
At this point we turned our attention to the application of IMDAF chemistry toward the construction of model systems. Furan was acetylated by treatment with a mixture of acetic anhydride and catalytic borontrifluoride etherate[188] and the resulting 2-acetylfuran converted to its corresponding Schiff base. The imine was reduced with sodium borohydride and the amide formed by activated ester coupling mediated by EDC.



Scheme 71.

Bis-furanamide **511** was subjected to a variety of conditions with the hope of effecting an intramolecular Diels-Alder closure. The molecule was stable up to greater than 200 °C. Compound **511** was also screened for possible reactivity promoted by Lewis acid catalysis. Lanthanide triflates, which are known to lower the LUMO and thereby facilitate Diels-Alder cyclizations, did not promote reaction in our case. Stronger Lewis

acids, such as dimethylaluminum chloride and aluminum chloride, resulted in complete decomposition of the bis-furan. We surmised that the constrained nature of the amide bond may force the molecule in such a conformation that the renders the Diels-Alder reaction unfavorable. Reduction of the amide to its amine would allow us to test this hypothesis. Amide **511** was reduced by LAH in ether to give the expected amine, which was subjected to several thermal Diels-Alder reactions without success.



511 **512**

Scheme 72.

The tandem oxidation-Diels-Alder sequence would have provided one of the most expedient routes to the core of thebaine. Though there is some precendent for thiophenes undergoing oxidation-mediated cycloadditions, the work described in this section is to the best our knowledge, the only attempts at intramolecular thiophene-based Diels-Alder reactions. Incomplete as they may be, these studies may provide a basis for further exploration in this area.

By examination of the early studies on chemical oxidation of thiophene by van Tilborg,[180] it would seem that the tendency of thiophines to undergo oxidative dearomatization is a strongly dependent on the nature of substitution on the ring. This work is summarized by the entries in Table 3. Moreover, mono-substituted thiophenes are not known to undergo oxidation without attendent decomposition. It is suspected that oxidation of mono-subsituted thiophenes may give rise to oxidation on the ring and

mixtures of subsequent ring-opened products. The stablest thiophene-1,1-dioxides are the most sterically congested; the dioxide corresponding to 2,5-di-*tert*-butylthiophene may even be handled in pure form. A number of chemical oxidation experiments (see Table 3) yielded complete decomposition of the starting material, and we speculated that this was probably due, at least in part, to the mono-substituted nature of the molecule and its tendency to decompose in the presence of strong oxidants.

The nature of the divalent sulfur in thiophene is altogether different than that of other sulfur-containing molecules. Thiophene is aromatic; its calculated resonance stabilization is slightly higher than that of furan or pyrrole.[189] As such, the divalent sulfur functionality is more difficult to oxidize than its non-aromatic analogues because its results eventually in dearomatization, a high energy process. To the best of my knowledge, only two reagents have been reported to carry out this transformation in thiophenes: dioxirane and *m*CPBA. In our hands, dioxirane (generated *in situ*) resulted in the re-isolated of unchanged starting material, while treatment of **497** or **502** with *m*CPBA gave the corresponding epoxides, isolated in 62 and 70% yields, respectively. Less reactive oxidants, such as $NaIO_4$ or $NaClO_2$ returned starting material unchanged. Finally, using oxidants in conjunction with acids, such as $RuCl_3$, $NaBO_4$, or MnO_2, often resulted in isomerization of the olefin into conjugation with the amide or ester.

The problems attributed to chemoselectivity in the oxidation of thiophene led us to adopt an alternative approach in which a furan nucleus would serve as a latent diene in an intramolecular furan Diels-Alder (IMDAF) approach toward thebaine. Gratifyingly, the bis-furanyl model system **511** was constructed in 8 steps in a strait-forward manner. We initially carried out a series of Lewis-acid promoted Diels-Alder reactions using

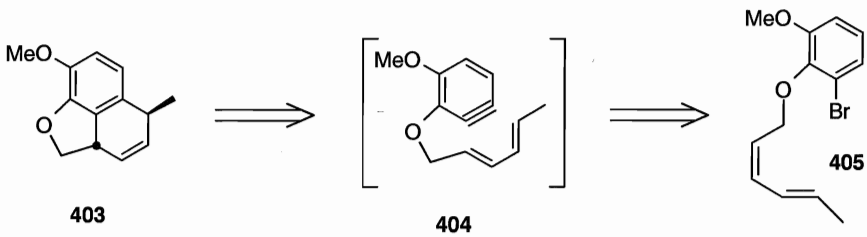
AlC_3, Me_2AlCl, $TiCl_4$, $Sc(OTf)_3$, $Yb(OTF)_3$, $CeCl_3$. Lanthanide triflates proved to be ineffective catalysts, while stronger acids, such as $AlCl_3$ and $TiCl_4$ resulted in destruction of the starting material. We decided at this stage to explore thermal cycloadditions of bis-furan **511** in the absence of Lewis-acid catalysts. Heating dilute (0.086 mmol) solutions of the amide failed to produce even trace amounts of the Diels-Alder adduct. We were concerned that the prescence of the amide functionality restrict the rotation of the molecule thereby causing it to adopt a conformation in which reaction could not take place. In order to test this hypothesis, the amide was reduced to its amine **512**, and the thermal Diels-Alder experiments were repeated. However, cyclization failed to occur even in excess of 200 °C! Future experiments may benefit from the use of a high pressure reaction vessel.

The original goal of the thiophene-based approach was to allow rapid access to the core of the morphinan skeleton based on our knowledge of enzymatic oxidations of aromatic and sulfur-containing compounds. The approach promised not only a viable entry into the morphine skeleton, but also an elegant solution to the generation of the C-13 quaternary center common to morphinan alkaloids. The failure of our original approach to deliver the target molecule prompted us to explore other routes which also have the potential to rapidly assemble the target molecule through Diels-Alder and palladium catalysis.

III-6.1.1 Alternative Diels-Alder Approach to Morphine

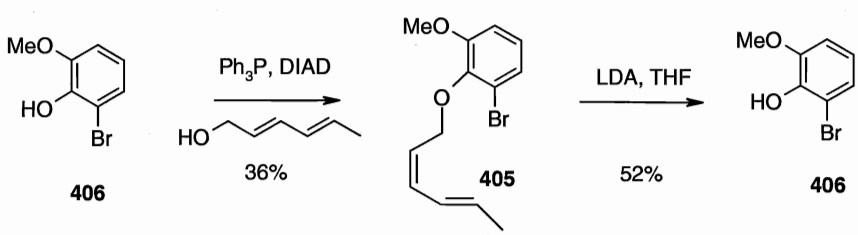
Despite the popularity of the Diels-Alder reaction, the analogous benzyne Diels-Alder reaction has seen little application in total synthesis efforts and relatively few examples of the intramolecular benzyne reaction exist. There are however, several

examples of the application of the benzyne Diels-Alder reaction as a key step in a total synthesis.[190]



Scheme 66. Retrosynthetic analysis of truncated morphinans by benzyne Diels-Alder reaction.

An initial model study was directed at determining the feasibility of a benzyne Diels-Alder reaction to establish the A, B, and D ring systems of morphine, Scheme 66. We envisioned that deprotonation of **405** at the position *ortho* to the bromine would allow generation of the benzyne **404**, which would be trapped in intramolecular fashion with the pendant dienyl tether. The benzyne precursor **405** was readily available through Mitsunobu alkylation of bromoguaicol with sorbyl alcohol.



Scheme 67.

Exposure of the material to LDA resulted in dealkylation to regenerate the starting phenolic compound. The approach was then abandoned in favor of the well-developed Heck and radical cyclizations previously carried out by the Hudlicky group.

III-6.2 Radical-Based Approaches to the Morphinan Skeleton

A new radical-based strategy was briefly investigated which would rely on a radical cascade closure to generate the C-13 quaternary center and "zip up" the A,B,and C ring system in a single operation. Following radical generation by heterolytic cleavage of the aromatic bromide, we imagined the possibility to establish the complete phenanthrofuran skeleton in a one-pot reaction by a radical cascasde terminating onto the aromatic alkyne.

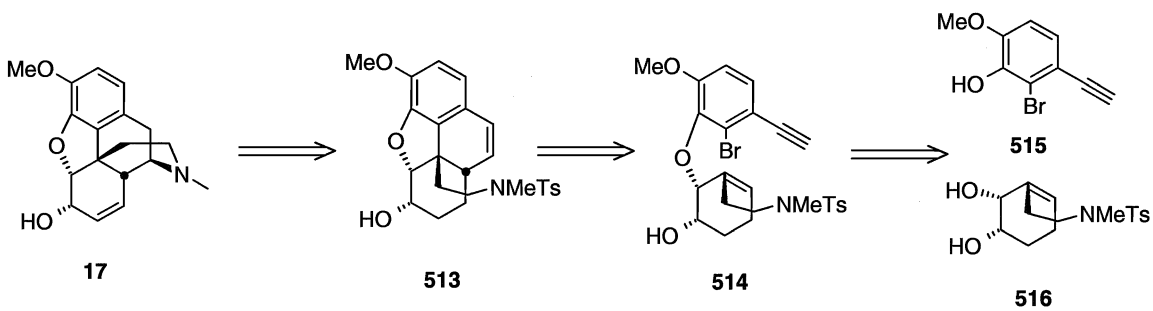
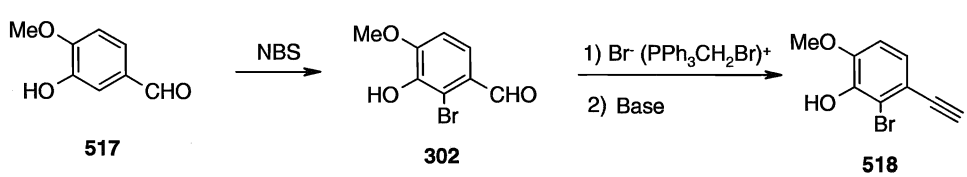


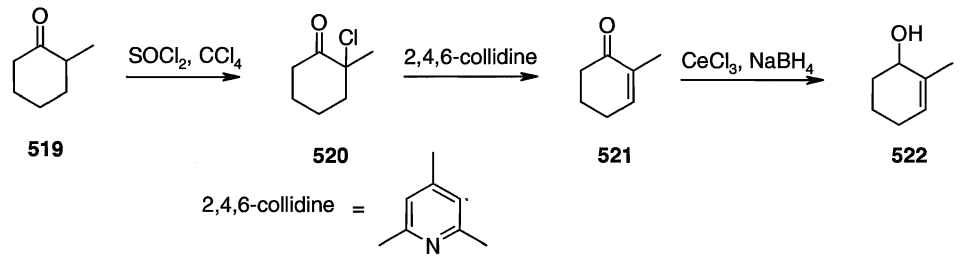
Figure 38. Retrosynthetic analysis of a radical-based approach to codeine.

In the event that the C-13 closure proceeded smoothly, a concern was the possibility for 5-exo vs. 6-endo closure onto the tethered alkyne. In cooperation with Dr. Takeo Omori, a model system was constructed to allow the investigation of this closure. The aromatic alkyne was available through bromination[191] of commercially available iso-vanillan, Corey-Fuchs homologation,[192] and elimination of the geminal dibromide to the corresponding alkyne.[193]



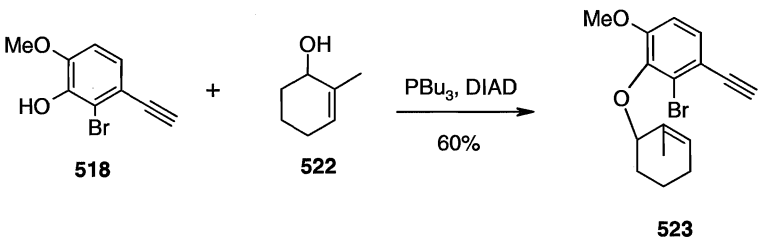
Scheme 74. Synthesis of aromatic alkyne.

The lower (C-ring) of the model system was synthesized in 3 steps from 2-methyl cyclohexanone, Scheme 75.



Scheme 75. Synthesis of allylic alcohol as C-ring analogue.

The first two steps of the sequence, an α-chlorination step, followed by a base-promoted elimination of the chloride to give the corresponding enone were described by W.S. Johnson.[194] A Luche reduction of the enone provided the requisite allylic alcohol **522**, which was ultimately coupled with the aromatic phenol by a Mitsunobu alkylation to provide a precursor for radical-promoted C-13 bond closure.



Scheme 76. Assembly of morphine model via Mitsunobu coupling.

Compound **523** was subjected to Parker's radical conditions (nBu$_3$SnH, AIBN, 0.012 M in toluene at 130 °C),[121] which gave a complex distribution of products. At least part of this mixture consisted of a bromine atom transfer across the alkyne. We did not, however, detect the product from 6-endo closure as we had originally hoped. The use of

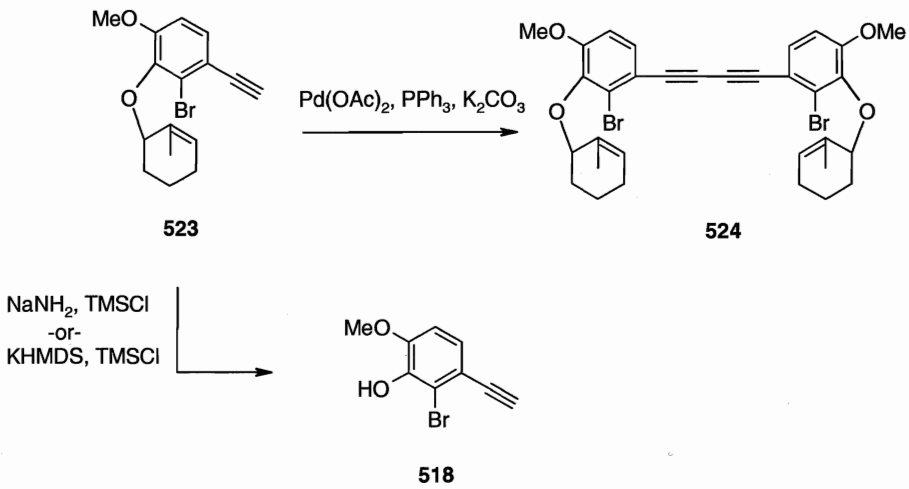
samarium diiodide as a source of radical initiation was evaluated; this reaction resulted in recovery of 96% starting material.

Although radical cascade reactions are shown to be powerful tools in the multi-step formation of carbon-carbon bonds, they have several drawbacks. Many reactions require the use of tributyltinhydride, giving rise to alkyltin by-products which can be difficult to separate from the desired reaction products. The radical closures onto alkynes are also complicated by 5-exo vs. 6-endo closures. The complicated reaction mixture resulting from radical-induced cascade reactions impelled us to re-visit anold theme-palladium catalysis as a strategic carbon-carbon bond forming reaction.

III-6.3 Palladium-Catalyzed Cyclization Studies in the Morphine Series

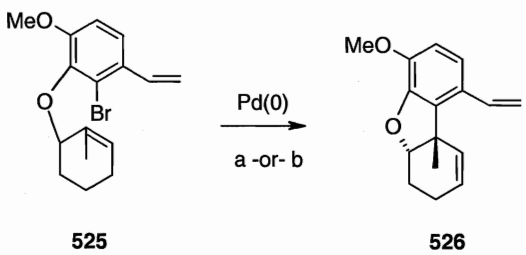
Owing to the non-stereospecific nature of radical closures in combination with complex product mixtures, the radical approach was abandoned in favor of Pd-catalyzed cyclizations. Such reactions have been employed in the construction of C-13 morphine centers previously (*vide supra*), and have the added advantage of generating a new site of unsaturation. Additionally, the model system **523** could be re-investigated using palladium to effect cyclization at the C-13 center.

Using $Pd(OAc)_2$ in conjunction with triphenylphosphine and potassium carbonate in DMF, compound **523** gave the corresponding *bis*-alkyne dimer **524** in 92% yield. A solution to the undesired coupling product could be realized by protection of the terminal alkyne, however, attempts to introduce a silyl protecting group onto the terminal position of the alkyne led to elimination of the phenol, Scheme 77.



Scheme 77.

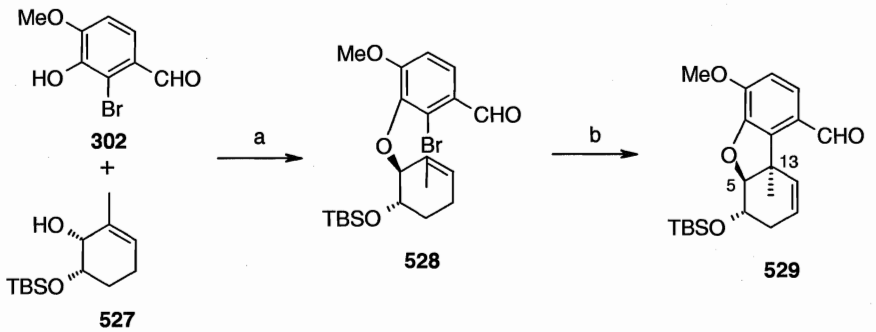
The Heck reaction was re-investigated with the corresponding alkene derivative **525**, which was prepared by Mitsunobu alkylation of the analogous alkene-substituted phenol. In these cases, the C-13 closure was accomplished, albeit in low yield, Scheme 78. A possible explanation to account for the low yield may be attributed to metallation of the allyl species, followed by elimination of the phenol. The phenol would have been washed away on work-up, and the cyclohexene moiety lost in evaporation with toluene.



Reagents and Conditions: a) $Pd(PPh_3)_4$ 0.1 equiv, Proton Sponge® 2.0 equiv, PPh_3, 0.3 equiv, benzene 11% yield, 19% starting material; b) $Pd(OAc)_2$ 0.1 equiv, PPh_3 0.3 equiv, K_2CO_3 3.0 equiv, DMF, trace of **526**, 15% starting material.

Scheme 78.

Encouraged by these initial results, we embarked on a more advanced model which would allow us to investigate a second Heck closure by Corey-Fuchs homologation of a pendant aldehyde, as detailed in Scheme 79. Recall that the requisite aldehyde is available by bromination of commercially available iso-vanillin. The allylic alcohol was synthesized from toluene in three steps by fermentation with *E. coli* JM 109 (pDTG601), reduction with diimide, and protection of the distal alcohol as its TBS-silyl ether.



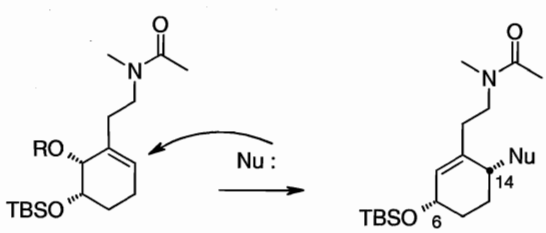
Reagents and Conditions: a) PBu_3 1.1 equiv, diisopropyl azodicarboxylate 1.1 equiv, 44%; b) $Pd(OAc)_2$ 0.15 equiv, dppf, 0.15 equiv, Ag_2CO_3 3.0 equiv, toluene, 62% yield.

Scheme 79. Optimized conditions for Heck closure.

We were now confident that the C-13 closure could be effected through an intramolecular Heck-type closure. An old problem soon presented itself- how to invert the C-5 center to permit synthesis of the natural enantiomer of morphine? Unwilling to lengthen the synthesis with tedious protection and inversion protocols, we looked for a route which would avoid inversion of the C-5 center of the starting diol. At this point, we turned again to palladium catalysis for the solution to the problem.

III-6.3.1 Allylic Displacement Approaches to Morphine Skeleton

Undoubtedly the most common criticism laid upon enzymatic chemistry is that it, in many cases, fails to deliver chiral synthons in either enantiomeric series. In the case of the enzyme toluene dioxygenase, however, Boyd and Hudlicky have independently developed routes to both enantiomers of the commonly-used bromodiene diol.[195,196] Unfortunately, this protocol has yet to be extended to the vast number of more sophisticated dienediols, which are largely available as single enantiomers only. While diene diols have shown great promise as synthons in morphine syntheses, previous syntheses have shown that the diol unit must be subjected to laborious inversion sequences in order to attach the requisite aromatic A-ring with correct stereochemistry. We attempted to circumvent this problem through either a Pd-promoted allylic acetate displacement, or alternatively through S_N2' displacement of an allylic carbonate.



530

R = OAc, CONHPh

531

Figure 39.

Such a displacement, if amenable to aromatic malonates or phenylacetylides, would provide easy access to morphine precursors in which the C-10-C11 bond had already been formed. As we had shown in our earlier model studies, the Heck reaction may then be used to forge the C-13 quaternary center. Finally oxidation of the alcohol at C-6 would permit installation of the benzofuran bridge using Gates protocol.[111]

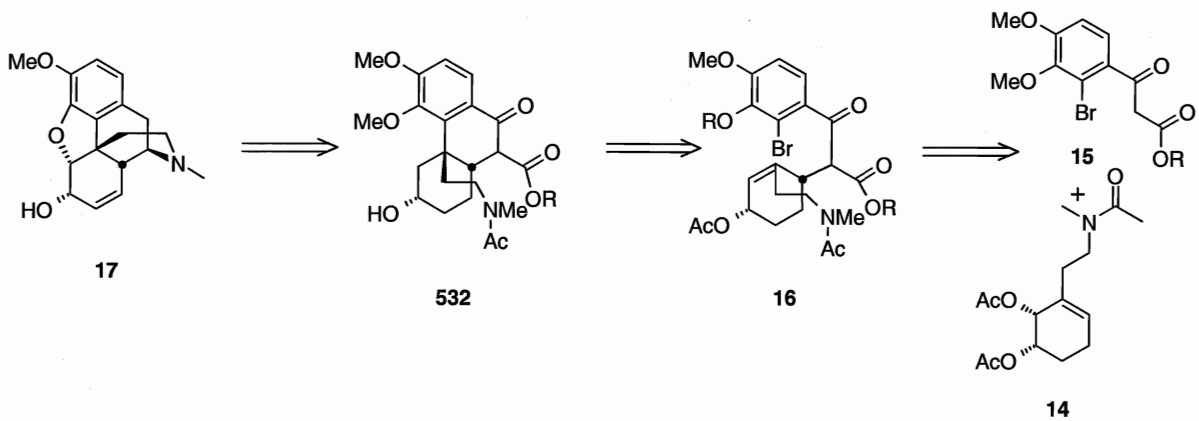
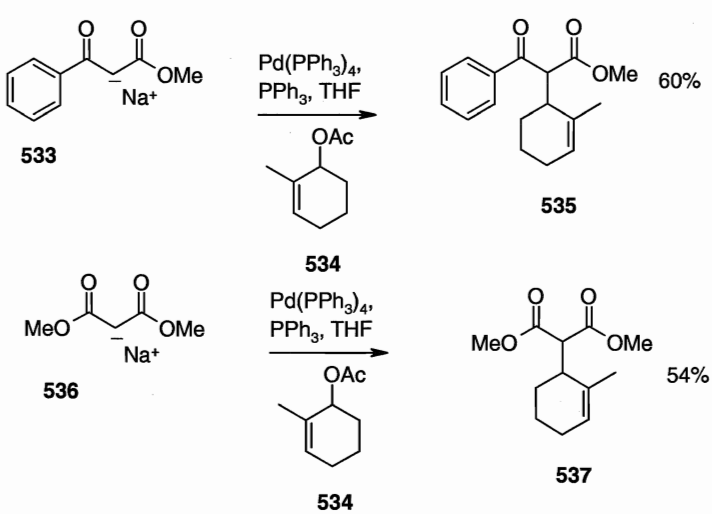


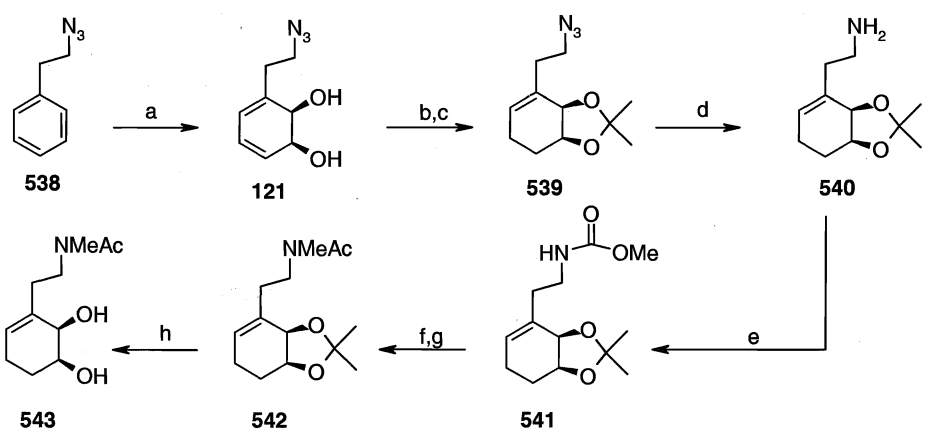
Figure 40. Retrosynthetic analysis of an allylic displacement approach toward morphinans.

Several groundwork experiments were carried out in order to establish the feasibility of the allylic acetate displacement approach. Allylic acetate **534**, prepared by acylation of allylic alcohol **522**, was treated with the anion of malonate **536**, or aromatic β-ketoester **533** in the presence of palladium (*tetrakis*)-triphenylphosphine in THF with triphenylphosphine as a supporting ligand. These conditions, originally reported by Trost,[197] provided the alkylated products in 54 and 60% yields, respectively. Encouraged by this initial result, a more elaborate allylic acetate was synthesized for further study.



Scheme 80. Model studies involving allylic acetate displacements.

Dienediol **121**, which carries the 8 carbons present in the lower portion of the natural product, was synthesized by enzymatic oxidation of azidoethylbenzene **538** with *E. coli* JM 109 (pDTG601). The *cis*-olefin in **121** was selectively reduced with diimide, and the diol functionality protected as its acetonide. The azide was converted to its amine by Staudinger[198] reduction with triphenylphosphine in aq THF. Next, the methylamine functionality was introduced by acylation of the primary amine with methyl chloroformate, and reduction of the resulting carbamate with lithium aluminum hydride in THF. After the nitrogen was protected as its acetate, we turned our attention to cleavage of the acetonide.

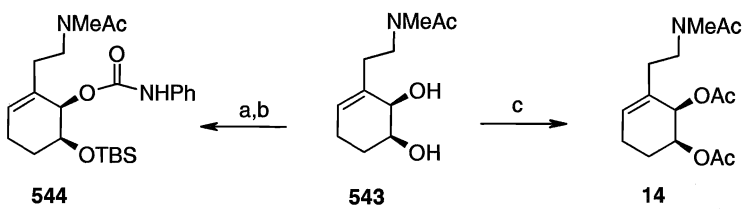


Reagents and Conditions: a) *E. coli* JM 109 (pDTG601A) (3.5 g/L); b) potassium azodicarboxylate, AcOH (60%); c) 2,2-dimethoxypropane, *p*TsOH, (quant); d) Ph_3P, H_2O, THF (78%); e) NEt_3, methyl chloroformate (52%); f) LAH, THF (quant); g) Ac_2O, DMAP, py (92%); h) 3:2:2 glacial AcOH/ H_2O/THF (74%).

Scheme 81. Initial synthesis of the C-ring.

Despite the number of existing protocols for facile removal of the acetonide protecting group, our attempts to effectively liberate the diol met with little success. Initially, the best results were obtained by treatment of compound **542** with 3% conc HCl in MeOH, which gave 45% yield (70% by conversion) in a single best experiment. Dowex-50-8

acidic resin gave complex mixtures and low yields of the free diol; treatment with silica gel in water at 150 °C returned only starting material. Ultimately, the protecting group was cleaved by treatment with 60% aq glacial acetic acid in THF (containing 1 drop of conc HCl) at refluxing temperature for 10 h, providing diol **543** in 74% yield. The diol was either elaborated to its carbamate **544** by protection of the distal hydroxyl as its TBS-silyl ether and subsequent treatment of the resulting alcohol with phenyl isocyanate in pyridine, or, simply converted to its corresponding triacetate **14** under standard conditions (Ac_2O, DMAP, TEA), Scheme 82.

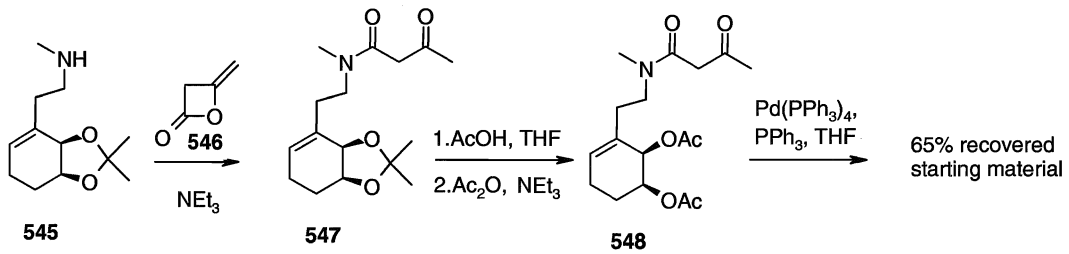


544 **543** **14**

Reagents and Conditions: a) TBS-Cl, imidazole, DMF (40%); phenyl isocyanate, DMAP, py (47%); c) Ac_2O, NEt_3, DMAP, CH_2Cl_2 (95%).

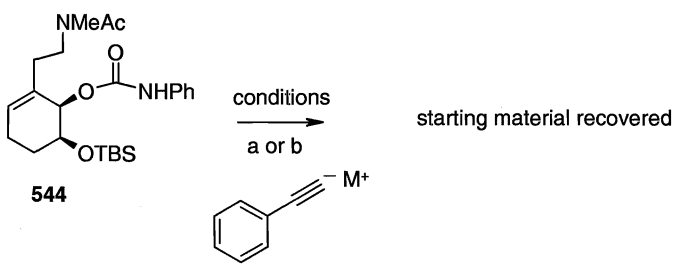
Scheme 82. Synthesis of allylic carbonates or acetates.

The allylic acetate displacement described by Trost was then re-investigated by Dr. Omori using the more advanced triacetate derivative **14**, whose synthesis is depicted in Scheme 82. Treatment of this substrate under Trost's conditions in the presence of the β-ketoester returned only starting material; decomposition to an unidentified mixture accompanied returned starting material in the case of attempted malonate displacement. In an attempt to further probe the displacement reaction, β-ketoamide **548** was synthesized, the anion was generated and allowed to react with palladium, according to standard conditions. In this case 65% starting material was recovered.



Scheme 83.

By consideration of Overman's S_N2' silylcuprate displacement of carbamates, and similarity between "softness" of acetylide anions and cuprates, we hoped the carbamate **544** would undergo displacement by the anion of phenylacetylene. This hypothesis was tested by reacting carbamate **544** with both the lithium and sodium anions of phenylacetylene, according to Scheme 84. No reaction was observed in either case at, or below, room temperature. In the case of the sodium anion, heating above 60 °C resulted in diminished yields of the recovered carbamate.

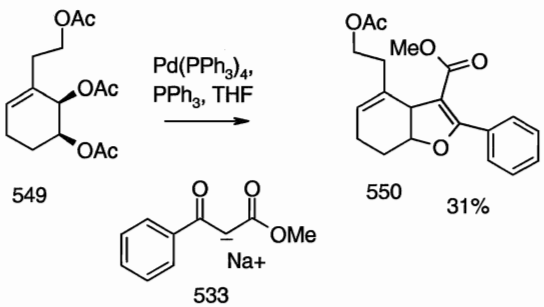


Scheme 84. Attempted carbamate displacement.

Reagents and Conditions: a) nBuLi, phenylacetylene, THF, -25 °C to rt, then 15 (75% recovered SM); b) NaH, phenylacetylene, THF, then 15, 0°C to 60 °C (33% recovered SM)

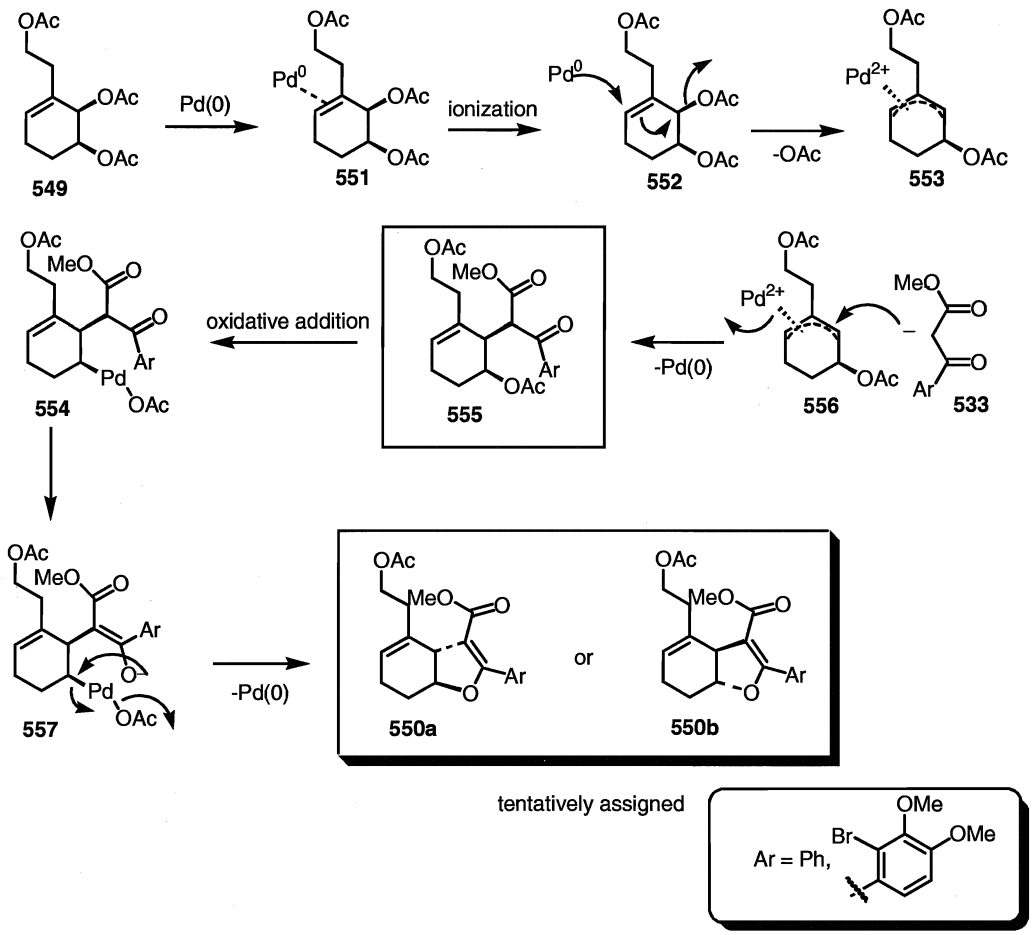
Now convinced that the problem with the displacement is somehow related to the amide functionality, we set out to prepare a synthetic equivalent of the amide to test in the

allylic displacement reaction. Surprisingly, the triacetate **549** reacted to give the the tetrahydrobenzofuran **550** in 31% isolated yield, Scheme 85.



Scheme 85.

A plausible mechanism for this unique transformation is outlined in Scheme 86. Initial complexation of the metal to the olefin leads to an ionized intermediate **553**, which is then attacked by the anion of the β-keto-ester, **533**. An insertion of Pd(0) into the carbon acetate bond gives **554**, which is prone to cyclization to furnish tetrahydrobenzofuran **550a** or **550b** as a single diastereomer and regenerating the active palladium catalyst in the process. The ring-junction stereochemistry of **550** is tentatively assigned as trans- based on the coupling constant (J = 8.4 Hz) and both possible trans-isomers are shown. Compound **550a** may result from initial π-complexation on the face opposite to the hydroxyl functionality, followed by an equilibration to the form a π-allyl complex occuping the same face as the hydroxyl. The equilibration step would lead to alkylation of the β-keto-ester with net inversion of configuration (note the initial stereochemistry of the triacetate). Diastereomer **550b** may result from initial π-allyl complex formation the less hindered face, permitting nucleophilic attack of the β-keto-ester to give net retention of configuration.

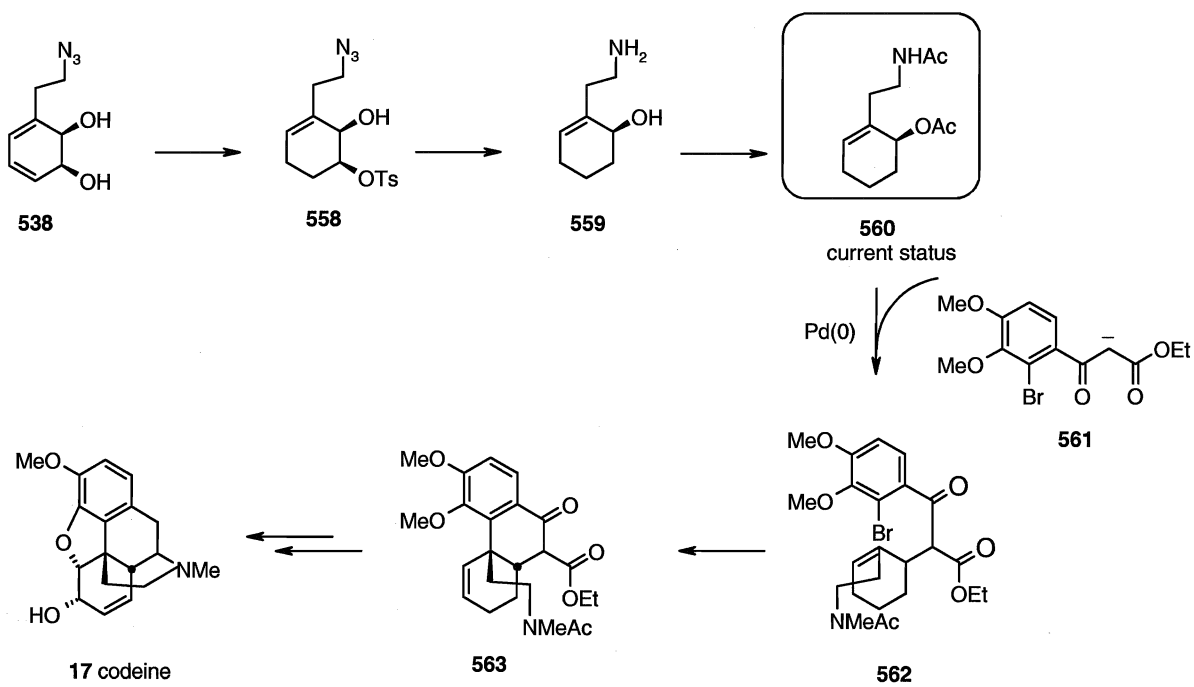


Scheme 86. Proposed mechanism for formation of tetrahydrobenzofurans under palladium catalysis.

IV. Conclusions and Future Work

Though unexpected, the isolation of compounds such as **550** is encouraging, as this route shows promise as a potential new entry into the morphine alkaloid family by forming the C-9/C-14 bond via palladium-mediated allylic acetate displacement and thus introducing carbons 9, 10, and the incipient ring A of morphine. When $Pd(allyl)_2Cl_2$ was used as a catalyst, compound **555** (Ar = dimethoxybromophenyl) was obtained along with recovered starting material. This is significant because such material may be used in

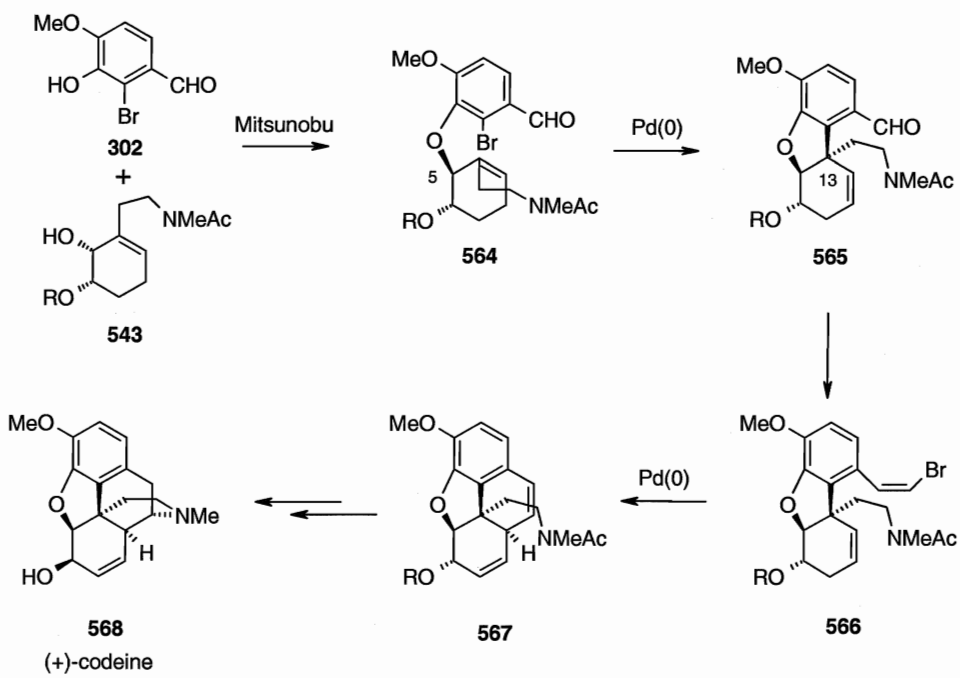
a Heck reaction to create the C-13 center. Future work may be divided into two categories. First, allylic acetate displacements by β-keto-ester nucleophiles will be re-investigated for compounds such as **560**, in which the distal hydroxyl functionality has been excised.



Scheme 87. Projected allylic acetate displacement and completion of codeine synthesis.

Removal of the distal hydroxyl should circumvent the formation of the benzofuran resulting from cyclization of the β-keto-ester. The requisite allylic acetate **560** was prepared from azidoethylbenzene according to Scheme 87. It is noteworthy to mention that compound **560** is quite similar to the allylic carbonates such as **303** used by Trost[6] in a palladium-mediated arylation reaction which comprised the enantioselective step in the synthesis of (-)-galanthamine and (-)-morphine (see Section II.3).

Second, the Heck reaction which succeeded in closing the C-13 center in previous model studies will be re-applied to a synthesis of unnatural (+)-morphine. This convergent approach will rely on a Mitsunobu alkylation to introduce the aryl fragment with inversion of configuration at C-5, thus allowing entry into the unnatural series of morphinan alkaloids via Heck reaction to establish the C-13 center. The homochiral C-ring, whose preparation has been detailed in Scheme 81, will be reacted with the appropriate aryl bromide, according to Scheme 88. The salient features of the proposed synthesis will entail a Heck closure to install the C-13 center, homologation of the aldehyde, and a subsequent Heck closure to form the phenanthrene core. Given the similarity between aldehyde **565** and Trost's aldehyde **308**, a concise asymmetric synthesis of synthesis of (+)-morphine should result from elaboration of the Heck product **565**. These projects are in progress and their current status as of this writing is indicated in Schemes 86, 87, and 88.



Scheme 88. Projected synthesis of (+)- morphine through Mitsunobu/ Heck strategy.

V. Experimental Section

General Experimental Section

All non-hydrolytic reactions were carried out under an argon atmosphere. Glassware used for moisture-sensitive reactions was flame-dried under vacuum and subsequently purged with argon. THF was distilled from potassium/benzophenone. Methylene chloride and acetonitrile were distilled from calcium hydride. Electrochemistry supplies and apparatus were purchased from EG&G Princeton Applied Research. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh). Analytical thin-layer chromatography was performed using silica gel 60-F_{254} plates. Melting points

were measured on a Thomas-Hoover melting point apparatus and are reported uncorrected. IR spectra were obtained on a Perkin-Elmer FT-IR 1600 Series Spectrum One instrument and were recorded as neat samples. ^{1}H and ^{13}C NMR spectra were obtained on either a 300-MHz Bruker or a 600 MHz Varian instrument. Specific rotation measurements are given in deg cm^3 g^{-1} dm^{-1} and were recorded on a Perkin-Elmer 341 Polarimeter. Ultraviolet spectroscopy was performed using a Perkin-Elmer 8452 A diode array spectrophotometer. Large-scale fermentation was performed in a 15-L B. Braun Biostat C-15 fermentor. All biological media was purchased through Sigma-Aldrich Canada. Combustion analyses were performed by Atlantic Microlabs, Norcross, Georgia, USA, and ISAR Laboratories, Guelph, Ontario, Canada.

General Experimental Procedures for Biotransformations

Small-scale fermentation with *E. coli* JM 109 (pDTG601)

Growth of colonies. Agar plates consisted of bactotryptone (10 g L^{-1}), yeast extract (5 g L^{-1}), NaCl (5 g L^{-1}), agar (30 g L^{-1}) and ampicillin (100 mg L^{-1}). *E. coli* JM 109 pDTG601 cells were streaked onto a plate and were incubated at 35 °C for 12-24 h. A single bacterial colony was selected for the preculture preparations described in the following section.

Preparation of preculture. Luria Bertani (LB) liquid medium consisted of bactotryptone (10 g L^{-1}), yeast extract (5 g L^{-1}), NaCl (5 g L^{-1}) and ampicillin (100 mg L^{-1}). The preculture medium (3 mL) was inoculated with a single colony of *E. coli* JM 109

(pDTG601) and the resulting inoculum was grown at 35 °C on an orbital shaker (200 rpm) for 6 h.

Fernbach flask preparation. LB liquid medium consisted of bactotryptone (10 g L^{-1}), yeast extract (5 g L^{-1}), NaCl (5 g L^{-1}), glucose (5 g L^{-1}) and ampicillin (100 mg L^{-1}). 500 mL of LB medium was inoculated with 1 mL of *E. coli* JM 109 (pDTG601) preculture medium. This inoculum was grown at 35 °C on an orbital shaker (180 rpm) for 5 h. A chemical inducer, isopropyl-1-thio-β-D-galactopyranoside (IPTG) (10 mg L^{-1}), was added via sterile filter and the cells were grown for additional 7 h at 35 °C on an orbital shaker (200 rpm).

Substrate Addition. The cells were separated from the supernatant by centrifugation at 7000 rpm for 15 min and the supernatant was decanted. The cell pellet was re-suspended in 500 mL of 0.1 M phosphate buffer consisting of KH_2PO_4 (6.8 g L^{-1}), K_2HPO_4 (8.7 g/L^1) and glucose (2 g L^{-1}). The aromatic substrate (400 mg L^{-1}) was added as a solution in isopropyl alcohol. Product formation was monitored by thin-layer chromatography (hexane-ethyl acetate, 1:1).

Product Isolation. After 5 h of incubation with substrate the pH of the culture medium was adjusted with 6 M NaOH to 8.5, and a cell pellet was obtained by centrifugation at 7000 rpm and 4 °C for 20 min. The supernatant liquid was extracted with acid-free ethyl acetate (prepared by stirring with a saturated solution of Na_2CO_3) and separation of the organic from the aqueous layer. The extract was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude material was purified by crystallization or flash column chromatography (silica gel deactivated with 10% distilled

water) immediately after concentration of the solvent in order to minimize decomposition of the unstable dienediols.

Large-scale fermentations were carried out in a 15-L (8-L working volume) B. Braun Fermentor according to a published procedure.[25]

Extraction of Products

Dienediols obtained from large-scale (8-L fermentation) were extracted from the aqueous fermentation broth into ethyl acetate either by standard manual extraction or by continuous extraction. The diene diols derived from small-scale fermentations (<1-L) were extracted manually. Progress of either manual or continuous extraction was monitored by thin layer chromatographic analysis of the aqueous layer.

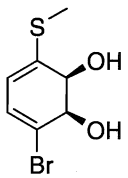
General Procedure for the Acitivation of Silica Gel:

Silica gel (1.5 g, 230-400 mesh) was poured onto a sintered glass Büchner funnel and washed with reagent grade THF (2 x 15 mL) and diethyl ether (2 x 15 mL). The silica gel was transferred to a round-bottomed flask and heated externally at 140 °C under vacuum (1 mm Hg) for 24 hours.

General Procedure for Opening of Aziridines and Epoxides on Silica Gel Surface:

A flame-dried 25-mL round-bottomed flask was charged with indole (1.2 mmol, 3 eq.), aziridine or epoxide electrophile (0.40 mmol, 1.0 eq.), and previously activated silica gel (500 mg). The starting materials were suspended in 3 mL freshly distilled methylene chloride and the solvent removed under reduced pressure. The silica gel supporting the adsorbed reactants was heated externally at 70 °C under argon atmosphere for 48 hours,

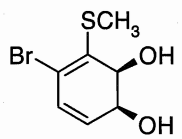
after which time the silica gel was loaded onto a flash silica gel column and the condensation product eluted with 4:1 hexanes/ethyl acetate.



(1*S*,2*R*)-3-Bromo-6-(methylsulfanyl)cyclohexa-3,5-diene-1,2-diol (316)

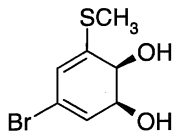
The biooxidation of 4-bromo-1-(methylsulfanyl)benzene **315** was performed according to the general procedure for large-scale fermentation. 4-bromo-1-(methylsulfanyl)benzene (35 g) was added as a slurry in a minimal amount of DMSO to a 15-L fermentor containing a growing culture of *E. coli* JM 109 (pDTG601) over a 2 h period. After stirring the media for an additional 2 h, the cell broth was separated from the cells by centrifugation. The broth was then extracted with equal volumes of ethyl acetate (20L x 2) until TLC analysis of the aqueous layer revealed that the extraction was complete. The combined organic were layers washed twice with 10 % (by volume) of saturated sodium carbonate solution to remove any residual phenol. The organic extracts of the fermentation broth were concentrated *in vacuo* and diol **316** precipitated by addition of pentane. Recrystallization from ethyl acetate/pentane provided the title compound as a white solid (18 g, 2.25 g/L): mp 59-63 °C; $[\alpha]\ ^{19}_{D}$ -10.0, (*c* 1.08, $CHCl_3$); R_f 0.26 (hexanes-ethyl acetate, 1:1); IR (film) ν 3197, 2921, 1626, 1548, 1416, 1340, 1306, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.37 (d, *J*= 6.1 Hz, 1H), 5.35 (d, *J*= 6.3 Hz, 1H), 4.43 (dd, *J* = 9.0, 3.2 Hz, 1H), 4.32 (dd, *J* = 7.5, 1.4 Hz, 1H), 2.63 (d, *J* = 9 Hz, 1H), 2.26 (s, 3H), 2.24 (d, *J* = 7.6, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.8, 127.8, 120.3, 112.7,

73.6, 72.5, 14.4; MS (EI) *m/z* (%): 238 (8), 236 (8), 220 (100), 218 (98), 205 (41), 203 (39), 177 (24), 175 (24), 157 (20), 142 (25), 109 (33), 96 (24), 45 (41); HRMS-EI calcd for $C_7H_9BrO_2S$ (M^+): 235.9501, found: 235.9506.



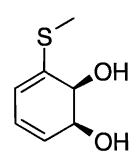
(1*S*,2*S*)-4-Bromo-3-(methylsulfanyl)cyclohexa-3,5-diene-1,2-diol (364)

Diol **364** was prepared according to the general procedure for shake-flask fermentation described above. 2-Bromophenyl methyl sulfide **363** (0.6 g, 2.97 mmol) was added to the *E. coli* JM 109 (pDTG601) culture, and product formation was monitored by TLC (R_f 0.3, 1:1, hexanes-ethyl acetate) and UV/Vis (λ_{max} 288 nm, 100X dilution, distilled H_2O as blank). The resulting yellow-white crystalline material was purified by column chromatography (96:4, CH_2Cl_2-MeOH), and the title compound (0.117 g, 16 %) was isolated as off-white solid: mp 70 °C; $[\alpha]_D^{22}$ +130 (*c* 1.0, MeOH); $[\alpha]_D^{22}$ +123 (*c* 1.0, MeOH)]; R_f 0.2 (96:4, CH_2Cl_2-MeOH); IR (film) ν 3258, 2924, 2871, 1259, 1101, 1095, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.9 (dd, J = 9.83, 2.56 Hz, 1H), 5.5 (d, J = 9.7 Hz, 1H), 4.4 (s, 1H), 4.1 (d, J = 5.3 Hz, 1H), 2.5 (s, 1H), 2.3 (s, 3H), 2.1 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.9, 129.8, 129.0, 116.6, 70.1, 68.7, 15.0; MS (EI) *m/z* (%): 238 (46.1), 236 (46.4), 220 (68.4), 218 (67.4), 111 (100), 109 (69.1), 81 (87.3); HRMS-EI calcd for $C_7H_9BrO_2S$ (M^+): 235.9506, found: 235.9501.



(1*S*,2*S*)-5-Bromo-3-(methylsulfanyl)cyclohexa-3,5-diene-1,2-diol (327)

3-Bromophenyl methyl sulfide **326** (0.4 g, 1.97 mmol) was added to a growing culture of *E. coli* JM 109 (pDTG601) according to the general procedure for shake-flask transformation described above. Product formation was monitored by TLC (R_f 0.5, 1:1, hexane-ethyl acetate). A yellow oily material was purified by column chromatography on 10% deactivated silica gel (hexane-ethyl acetate, 1:1), and the title compound was isolated as off-white solid, (7 mg, 1.6 %). Mp 87-89 °C; $[\alpha]_D^{23}$ +26.6 (*c* 0.88, acetone) R_f 0.5 (hexane-ethyl acetate, 1:1). IR (film) ν 3350, 3019, 2917, 1603, 1551, 1435, 1384, 1216, 1112, 1043 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.0 (d, J = 2.7 Hz, 1H), 5.4 (s, 1H), 4.1 (m, J = 9.8, 6.2, 4.4 Hz, 2H), 2.2 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.7, 124.8, 118.9, 116.3, 70.7, 69.5, 13.0; MS (EI) *m/z* (%): 238 (10.2), 236 (10.3), 220 (100), 218 (97.2), 205 (42.2), 203 (40.8), 177 (18.8), 175 (18.4), 111 (40.5), 95 (25.1); HRMS-EI calcd for $C_7H_9BrO_2S$ (M^+): 235.9507; found, 235.9509.



(1*S*,2*S*)-3-(methylsulfanyl)cyclohexa-4,6-diene-1,2-diol (349)

a) **Preparation from diol 316 by electrochemical reduction**:

Electrolysis was performed in a 150 mL beaker with a mercury pool cathode and Ag/Ag^+ (silver wire in a solution of 0.1 M $AgNO_3$ in acetonitrile) as reference electrode. A Pt anode was placed in a chamber separated from the rest of the cell by a sintered-glass frit.

Dienediol **316** (237 mg, 1 mmol) was dissolved in a minimum amount of acetonitrile and transferred to the beaker containing 100 mL of 0.15 M Et_4NBr solution in acetonitrile (previously degassed under positive pressure of argon for 20 min) followed by tetrabutylammonium hydroxide (1 mL of 40% aqueous solution). Electrolysis was performed at -2.75 V. A charge of 2 *F*/mol was delivered over approximately a 1 h period; progress of the reaction was monitored by TLC. Following electroreduction, the crude reaction mixture was decanted, and 10 mL of saturated sodium carbonate solution was added to neutralize any phenolic residue formed as a byproduct of the reaction. The organic solvent was evaporated under reduced pressure, and the residue diluted with 20 mL of distilled water. The aqueous layer was extracted with 5×50 mL of diethyl ether. The combined ethereal layers were washed with 2×3 mL of saturated sodium carbonate, 10 ml of brine and dried over anhydrous $MgSO_4$. After filtration to remove the drying agent, the solvent was removed under reduced pressure, and the crude product was immediately purified by flash chromatography on deactivated silica gel (hexanes-ethyl acetate, 6:4). Purification afforded the title compound as a white crystalline solid, 31.1 mg (20%). The crystalline product decomposes completely to its phenolic derivative at room temperature in less than 30 min; however, in dilute dichloromethane solution the decomposition is significantly slowed and the dienediol is stable for several days. Mp 61-62 °C; $[\alpha]^{24}_D$ +81.3, (*c* 0.27, MeOH); (lit:[199] $[\alpha]_D$ +37 (c 0.7, MeOH)); R_f 0.4 (hexanes-ethyl acetate, 30:70). IR (film) ν 3247, 2915, 2858, 1551, 1545, 1431, 1420, 1321, 1292, 1106 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ: 5.99 (dq, *J* = 5.5, 2 Hz, 1H), 5.72 (dd, *J* = 9.5, 3.6 Hz, 1H), 5.58 (d, *J* = 5.6 Hz, 1H), 4.25 (m, 1H), 4.02 (d, *J* = 5.5 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ: 141.7, 125.4, 124.5, 114.0, 71.3, 69.1, 13.0. Note:

b) **Preparation from diol 316 by Heck reduction**:

To a thick-walled reaction vessel equipped with magnetic stirring bar and Teflon seal was added dienediol **316** (300 mg, 1.27 mmol, 1 equiv), 5% palladium on activated carbon (60 mg), and freshly distilled triethylamine (500 μL, 3.8 mmol, 3 equiv). The reaction vessel was flushed with argon before addition of formic acid (120 μL, 2.8 mmol, 2.2 equiv). The vessel was sealed and the reaction mixture stirred at rt for 1 h and then heated for 2 h at 55 °C. The crude mixture was filtered through Celite and washed with 5 mL of methanol. The crude product, which is unstable, was used directly in the subsequent reaction without further purification.

c) **Preparation from diol 327 by Heck reduction:**

To a thick-walled reaction vessel equipped with magnetic stirring bar and Teflon seal was added dienediol **327** (25 mg, 0.11 mmol, 1 equiv), 5% palladium on activated carbon (15 mg), and freshly distilled triethylamine (87 μL, 0.63 mmol, 5.7 equiv). The reaction vessel was flushed with argon before addition of formic acid (8 μL, 0.46 mmol, 4 equiv). The vessel was sealed and the reaction mixture was stirred at rt for 10 min and then heated for 1 h at 55 °C. The crude mixture was filtered through Celite and washed with 5 mL of methanol. The crude product, which is unstable, was used directly in the subsequent reaction without further purification.

(1*S*,2*S*)-3-(methylsulfanyl)cyclohex-3-ene-1,2-diol (350)

a) **By diimide reduction of diene 349**:

The crude product (1 mmol) from electroreduction was chromatographed on 10%-deactivated silica (hexanes-ethyl acetate, 30:70). Fractions containing the pure dienediol (TLC analysis) were transferred to a round-bottomed flask containing 10 mL methanol, and the hexanes/ethyl acetate mixture was evaporated with continuous addition of methanol. When the solvent volume was reduced to approximately 30 mL, the flask was placed in an ice/salt bath. Potassium azodicarboxylate (580 mg, 3.0 mmol, 3 equiv) was added in portions to the methanolic solution. Upon complete addition of the PAD reagent, the yellow slurry was stirred for 10 min. Acetic acid, (400 μL, 7 mmol, 7 equiv) in 15 mL methanol was added dropwise over a two hour period to the slurry at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The pH of the mixture was brought to neutral by addition of 4 mL of saturated solution of sodium hydrogencarbonate. Methanol was removed under reduced pressure and the residue diluted with 5 mL of distilled water followed by 20 mL of ethyl acetate. The layers were separated, and the aqueous layer extracted three times with 20 mL portions of ethyl acetate. The combined organic layers were dried (anhydrous $MgSO_4$) and the solvent removed under reduced pressure to afford the title compound as a white crystalline solid, 37 mg (16 % yield over two steps). The crude product may be further purified by recrystallization from methylene chloride/pentane. Mp 91-93 °C; $[\alpha]_D^{24}$-104, (*c* 0.75, $CHCl_3$); R_f 0.4 (hexanes-ethyl acetate, 30:70); IR (film) ν 3249, 2944, 2913, 2890, 2829,

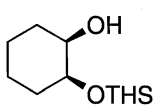
1623, 1434, 1356, 1327, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.57 (t, *J* = 4 Hz, 1H), 4.05 (s, 1H), 3.82 (d, *J* = 4.2 Hz, 1H), 2.55 (d, *J* = 4.1 Hz, 1H), 2.40 (s, 1H), 2.19 (s, 3H), 2.15-2.10 (m, 1H), 1.85-1.60 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.6, 124.8, 69.4, 69.1, 25.7, 24.8, 15.1; MS (EI) *m/z* (%): 160 (50), 142 (22), 127 (31), 116 (100), 95 (47), 87 (58), 68 (40,), 55 (30), 45 (54); HRMS-EI calcd for $C_7H_{12}O_2S$ (M^+): 160.0554, found: 160.0558; Anal. Calcd for $C_7H_{12}O_2S$: C, 52.47; H, 7.55; Found C, 52.74; H, 7.39.

b) **An alternative procedure for the reduction of unstable diene diol 349 from the Heck reduction product 349**:

A 50-mL round-bottomed flask fitted with an addition funnel was charged with the crude debrominated material **349** dissolved in 5 mL of methanol. The reaction flask was placed in an ice bath and PAD reagent (730 mg, 3.8 mmol, 3 equiv) added in 2 portions. After 10 min, a solution of acetic acid (493 μL, 8.89 mmol, 7 equiv) in 10 mL of methanol was added to the yellow slurry over a 45 min period. The reaction mixture, whose yellow color gradually faded to tan, was allowed to warm to rt overnight. The reaction mixture was neutralized with a saturated solution of sodium hydrogencarbonate. After neutralization, the volume of the reaction mixture was reduced to approximately half under reduced pressure. The contents of the reaction flask were extracted with several portions of ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous MgSO4. Removal of the organic solvent under reduced pressure provided a tan solid (57 mg, 28 % over two steps), whose spectral data were consistent with that previously published.

c) **Preparation from diol 349 (prepared by Heck reduction of *m*-bromothioanisole diol 327):**

To a 25-mL round-bottomed flask equipped with an addition funnel and magnetic stirring bar was added crude debrominated material **349** dissolved in 5 mL of methanol. The reaction flask was placed in an ice bath and potassium azodicarboxylate (73 mg, 0.38 mmol, 3 equiv) added in 2 portions. After 10 min, a solution of acetic acid (53 μL, 0.88 mmol, 7 equiv) in 3 mL of methanol was added to the yellow slurry over 30 min. The reaction mixture was allowed to warm to rt overnight and neutralized with a saturated solution of sodium hydrogencarbonate. After neutralization, the volume of the reaction mixture was reduced to approximately half under reduced pressure. The content of the reaction flask was extracted with several portions of ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous MgSO4. Removal of the organic solvent under reduced pressure gave the crude diol **5**, which was purified by flash column chromatography to furnish 1 mg of the title compound; $[\alpha]_D^{21}$ -35, (*c* 0.1, $CHCl_3$); lit[136]: $[\alpha]_D^{24}$-104, (*c* 0.75, $CHCl_3$).



(1R,2S)-2-[(Hexyldimethylsilyl)oxy]cyclohexan-1-ol (358)

a) **Preparation from vinyl bromide 357 (derived from homochiral bromodienediol 72)**

A hydrogenation flask was charged with bromide **357** (1.0 g, 2.9 mmol, 1 equiv), triethylamine (0.40 mL, 2.9 mmol, 1 equiv), platinum oxide (Adams catalyst, 65 mg, 0.29 mmol, 0.10 equiv) and 5 mL of methanol. The flask was placed in a Parr hydrogenation apparatus, slowly evacuated, and the headspace filled with hydrogen gas. The flask was shaken for 2 h under 3 atm hydrogen. When the reaction was complete by TLC analysis,

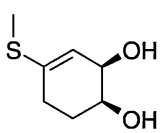
the catalyst was removed by filtration through a short plug of Celite and sand. The solvent was evaporated, and the residue diluted with 1 mL water, 10 mL ethyl acetate, and extracted. The organic layer was washed with water (2 mL x 2), sat. $NaHCO_3$ (2 mL x 2), brine, (2 mL x 2), and dried (anhydrous $MgSO_4$). Removal of the solvent provided the title compound as a clear and colorless oil (735 mg, 98 %); $[\alpha]_D^{23}$ +10.6, (*c* 1.0, $CHCl_3$); R_f 0.55 (hexanes-ethyl acetate, 9:1); IR (neat) ν 3580, 3487, 2938, 2866, 1463, 1447, 1377, 1252, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.62 (dt, J = 7, 3 Hz, 1H), 3.51 (m, 1H), 2.05 (bs, 1H), 1.7-1.3 (m, 8H), 0.77 (dd, J = 6.8, 2 Hz, 6H), 0.72 (s, 6H), 0 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 74.4, 73.0, 36.6, 32.9, 32.5, 24.4, 22.7, 22.5, 21.0, 20.9, 0, -0.5; MS (EI) *m/z* (%): 173 (19), 155 (2), 129 (2), 105 (6), 81 (13), 75 (35), 55 (4), 41 (6); HRMS-EI calcd for $C_8H_{17}O_2Si$ (M^+): 173.10195, found: 173.09933.

b) **Preparation of 358 from thioether 350**:

A 5-mL round-bottomed flask was charged with diol **350** (75 mg, 0.46 mmol, 1equiv), imidazole (41 mg, 0.61 mmol, 1.3 equiv), and 400 μL of anhydrous DMF. The flask was cooled to -30 °C, then THS-Cl (87 μL, 0.49 mmol, 1.05 equiv) was added. The mixture was stirred at -30 °C for 1 h and then the reaction flask was placed in a freezer (-18 °C) for 10 h. The mixture was diluted with 30 mL of ether, washed with 8 x 1 mL of aqueous solution of 5% citric acid, 2 x 1 mL brine, and the ethereal layer dried over anhydrous $MgSO_4$. The drying agent was removed by filtration, and the solvent was removed under reduced pressure to afford the crude silyl ether, (120 mg, 90 % crude yield) which was used directly in the subsequent reaction without further purification.

Commercially available Raney nickel 2400® was activated by swirling with 10% NaOH solution and decanting the supernatant. The procedure was repeated with distilled water

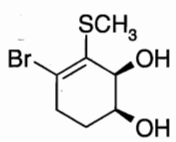
until neutral pH was attained (about 12 washes). The nickel was finally washed with absolute ethanol three times. The crude THS-protected thioether **360** (60 mg, 0.199 mmol) was introduced into a 25-mL round-bottomed flask equipped with a magnetic stirring bar and reflux condenser. The reaction flask was then charged with freshly activated Raney Ni (spatula tip) and 5 mL absolute ethanol. The reaction flask was heated to maintain steady reflux overnight. Reaction progress was monitored by TLC and the reaction deemed complete after 11 h at reflux temperature. The reaction mixture was filtered through a plug of Celite and washed with copious amounts of hot methanol. The washings were passed through a plug of silica gel to remove residual impurities. The product was obtained as yellow oil, 15 mg (29% yield). ^{1}H and ^{13}C NMR spectral data matched those of compound **358**, prepared by hydrogenation of vinyl bromide **357**.



(1*S*,2*S*)-4-(methylsulfanyl)cyclohex-3-ene-1,2-diol (355)

To a flame-dried flask containing a magnetic stirring bar was added bromide **351** (1.0 g, 5.18 mmol, 1 equiv), sodium methanethiolate (725 mg, 10.4 mmol, 2 equiv), and 3 mL of HMPA under argon atmosphere. The reaction flask was heated to an external temperature of 65 °C for a period of 16 h. The crude reaction mixture was taken up in 50 mL of diethyl ether and washed with water (1mL x 10) and brine (1mL x 2). The ethereal layer was dried (anhydrous $MgSO_4$), the drying agent filtered, and the solvent removed under reduced pressure to provide a brown oil which was purified by silica gel flash chromatography (hexanes-ethyl acetate, 30:70). The title compound was isolated as a crystalline white solid (24%). Mp 83 °C; $[\alpha]^{24}_{D}$ -74 (*c* 0.75, $CHCl_3$); R_f 0.32 (hexanes-

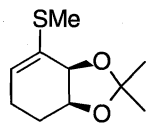
ethyl acetate, 30:70); IR (film) ν 3247, 2914, 1432, 1294, 1123, 1100, 996 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.25 (d, J = 4.1 Hz, 1H), 4.12 (m, 1H), 3.78 (m, 1H), 2.75-2.4 (bs, 2H), 2.30-2.05 (m, 2H), 2.17 (s, 3H), 1.85-1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.1, 116.2, 68.9, 67.3, 28.3, 26.7, 14.4; MS (EI) *m/z* (%): 160 (39), 142 (64), 127 (31), 116 (72), 109 (30), 101 (100), 85 (24), 69 (49), 53 (22), 41 (41); HRMS-EI calcd for $C_7H_{12}O_2S$ (M^+): 160.0565, found, 160.0556; Anal. Calcd for $C_7H_{12}O_2S$: C, 52.47; H, 7.55, Found, C, 53.02; H, 7.82.



(1*S*,2*S*)-4-Bromo-3-(methylsulfanyl)cyclohexa-3-ene-1,2-diol

Diol **364** (0.63 g, 3.0 mmol) was dissolved in 35 mL MeOH, and the round-bottomed flask containing the solution was subsequently placed into an ice/NaCl bath. PAD reagent (1.8 g, 9.0 mmol) was added in portions to the methanolic solution. The resulting yellow slurry was stirred for 15 min, at which point acetic acid (1.2 mL, 21 mmol) in 25 mL MeOH was added dropwise *via* addition funnel over a period of 3 h. The reaction mixture was allowed to warm to rt overnight. The pH of the reaction mixture was brought to slightly alkaline by adding 20 mL of saturated $NaHCO_3$ solution. Methanol was removed under reduced pressure and the residue diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted with several portions of ethyl acetate. The combined organic layers were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered, and solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (CH_2Cl_2-MeOH, 96:4) yielding the

title compound as white solid, 0.321g (51 %). Mp 135 °C; $[\alpha]_D$ -104.3 (*c* 0.5; acetone); R_f 0.2 (96:4, CH_2Cl_2-MeOH). IR (film) ν 3401, 2977, 2400, 1604, 1521, 1476, 1424, 1216, 669. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.3 (s, 1H), 3.9 (s, 1H), 2.4 (s, 3H), 2.3 (s, 3H), 1.9 (m, 2H), 1.8 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.7, 121.4, 69.1, 68.7, 36.4, 26.9, 13.4; MS (EI) *m/z* (%): 240 (17.5), 238 (18.4), 196 (30.0), 194 (30.1), 149 (100); HRMS-EI calcd for $C_7H_{11}BrO_2S$ (M^+): 237.9663; found: 237.9661; Anal. Calcd for $C_7H_{11}BrO_2S$: C, 35.16; H, 4.64, Found: C, 35.48; H, 4.30.



(3a*S*,7a*S*)-2,2-Dimethyl-4-(methylsulfanyl)-3a,6,7a-tetrahydro-1,3-benzodioxole (366)

a) **Preparation from diol 350**:

Diol **350** (55 mg, 0.35 mmol, 1 equiv) was transferred to a 10-mL round-bottomed flask and dissolved in 1 mL of acetone. 2,2-DMP (250 μL, 2.0 mmol, 5.7 equiv) was added followed by 1 crystal of *p*TsOH. The solution was stirred at rt for 24 h before the reaction was quenched with 1 mL of a saturated $NaHCO_3$ solution. The cloudy mixture was diluted with 15 mL ethyl acetate and 2 mL of distilled water. The layers were separated and the aqueous layer back-extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to provide a tan oil (24 mg) which was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford the title compound as a clear oil, 16 mg (23 %). $[\alpha]_D^{22}$ +20.1 (*c* 0.8, $CHCl_3$); R_f 0.38 (10% ethyl acetate in hexanes). IR (film) ν 2984, 2924, 1624, 1438, 1379 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (s,

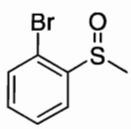
1H), 4.40 (s, 1H), 4.29 (s, 1H), 2.20 (s, 3H), 2.20 (m, 1H), 2.0-1.8 (m, 2H), 1.75-1.60 (m, 1H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.0, 123.8, 109.2, 74.5, 74.1, 28.1, 26.6, 25.9, 22.0, 14.9; HRMS-EI (M^+) calcd for $C_{10}H_{16}O_2S$, 200.0871; found, 200.0864; Anal Calcd for $C_{10}H_{16}O_2S$: C, 59.97; H, 8.05, Found: C, 60.11; H, 7.78.

b) **Preparation from the partially reduced diol derived from *o*-bromothioanisole 364**:

(1*S*,2*S*)-4-Bromo-3-(methylsulfanyl)cyclohexa-3-ene-1,2-diol (0.020 g, 0.084 mmol, 1 equiv) was dissolved in 2,2-DMP (1 mL, 8.4 mmol, 10 equiv), to which one crystal of *p*TsOH was then added. The reaction mixture was stirred at room temperature under a positive pressure of argon until the complete consumption of starting material was observed by TLC analysis (ca 1 h). R_f 0.9 (1:1, hexane-ethyl acetate). The solvent was removed under reduced pressure and the residue diluted with 0.5 mL of saturated $NaHCO_3$. The aqueous portion was extracted into ethyl acetate, washed with a saturated solution of NaCl, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and residual white-yellow solid dried under high vacuum. The protected diol **365** was used directly in the subsequent reaction without further purification.

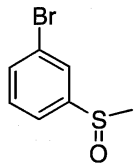
The crude material from the previous reaction was dissolved in 1 mL of anhydrous THF in a flame-dried 25-mL round-bottomed flask and cooled to -60 °C. *n*BuLi (195 μL of 1.6 M in hexanes, 0.25 mmol, 3 equiv) was added dropwise and the reaction mixture stirred at -60 °C under positive pressure of argon for 45 min. Reaction progress was monitored by TLC. The reaction mixture was quenched with 0.5 mL of distilled water and 1 mL saturated aqueous solution of ammonium chloride. The mixture was extracted several times with ether and the ethereal layer then washed with brine and dried over anhydrous

$MgSO_4$. The drying agent was removed by filtration and the solvent removed under reduced pressure to provide a crude oil which was purified by flash column chromatography (hexanes-ethyl acetate, 9:1), affording the title compound as a clear, colorless oil (3 mg, 18 %). $[\alpha]_D$ +20.3 (c 0.3, $CHCl_3$). IR (film) ν 3368, 2984, 2924, 1625, 1576, 1439, 1368, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.5 (s, 1H), 4.4 (s, 1H), 4.2 (s, 1H), 2.2 (s, 3H), 2.2 (m, 1H), 1.9 (m, 2H), 1.7 (m, 2H), 1.35 (s, 3H), 1.31 (s, 3H).



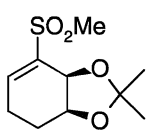
(+)-(*R*)-2-Bromophenyl methyl sulfoxide (363)

Sulfoxide **363** was prepared according to the general procedure for shake-flask fermentation described above. The crude material isolated after extraction was purified by column chromatography (CH_2Cl_2-MeOH, 96:4,) to give 2-bromophenyl methyl sulfoxide **363** (0.047 g, 7 %) as a brown oil. Further elution gave starting material (0.070 g, 0.346 mmol, 11%) and the chiral diene diol **364** (0.210 g, 0.890 mmol, 33%). $[\alpha]_D^{23}$ +32.5 (*c* 1.8, $CHCl_3$); lit.[146] $[\alpha]_D$ +35 (*c* 1.8, $CHCl_3$)]; R_f 0.4 (CH_2Cl_2-MeOH, 96:4); IR (film) ν 3400, 3059, 2996, 1447, 1093, 1058, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.9 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.5 (t, *J* = 17.2, 8.6 Hz, 2H), 7.2 (td, *J* = 7.8, 1.4 Hz, 1H), 2.7 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.3, 131.9, 131.3, 127.7, 124.7, 117.4, 40.9; MS (EI) *m/z* (%): 220 (81.6), 218 (84.4), 205 (100), 203 (98.7), 96 (33.8). HRMS-EI Calcd for C_7H_7OSBr (M^+): 217.9401; found: 217.9398.



(+)-(*R*)-3-Bromophenyl methyl sulfoxide (328)

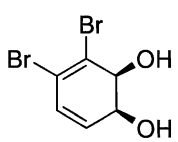
m-Bromothioanisole **326** (0.4 g, 1.97 mmol) was added to *E. coli* JM 109 (pDTG601) culture according to the general procedure described for shake-flask fermentation. Progress of the reaction was monitored by TLC. The crude material was purified by column chromatography (1:1, hexane-ethyl acetate) to provide 3-bromophenyl methyl sulfoxide **328** (0.130 g, 0.6 mmol, 28%) as a yellow oil. $[\alpha]_D^{23}$ +39.8 (*c* 1.2, acetone); lit.[147] $[\alpha]_D$ +116.3 (*c* 1.2, acetone)]; R_f 0.2 (hexane-ethyl acetate, 1:1). IR (film) 3440, 3054, 2998, 2912, 2856, 2094, 1959, 1885, 1709, 1643, 1567, 1460, 1402, 1080, 784 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.8 (s, 1H), 7.6 (td, J = 9.2, 1.1 Hz, 2H), 7.4 (t, J = 15.7, 7.9 Hz, 1H), 2.6 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.3, 133.9, 131.5, 126.5, 123.2, 122.9, 43.7; EI-MS *m/z* (%): 220 (83.4), 218 (83.3), 205 (100), 203 (97.6), 177 (10.4), 175 (12.0), 157 (24.8), 155 (25.4), 139 (21.0), 108 (22.2), 96 (23.0), 50 (44.4). EI-HRMS calcd. for C_7H_7BrOS (M^+): 217.9401; found: 217.9396.



2,2-Dimethyl-7-methylsulfone-3(*S*)a,4(*S*),5,7a-tetrahydro-benzo[1,3]dioxole (367)

Protected sulfide diol **366** (220 mg,1.14 mmol, 1 equiv) was suspended in a minimal amount of 50% $_{(aq)}$ acetone. To 0.4 mL 0.3 M aqueous ammonium molybdate solution was added 2.5 mL 30% $_{(aq)}$ hydrogen peroxide, and the resulting yellow solution was

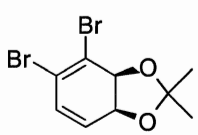
immediately added to the suspension of sulfide. Within seconds the reaction mixture became homogenous. The progress of the reaction was monitored by TLC and deemed complete after 3 min, at which time the reaction was quenched by addition of 3 mL saturated solution of sodium bisulfite until the reaction mixture confirmed a negative potassium iodide starch paper. The organic solvent was removed under reduced pressure and the aqueous portion extracted with chloroform (5 x 20 mL). The extract was dried ($MgSO_4$) and the solvent removed in vacuo to provide a crude oil. Purification by flash column chromatography (ether-pentane, 1:2) gave the title compound as a white crystalline solid (167 mg, 59% yield). Mp 84/85° C; $[\alpha^{23}{}_D]$ +98.1 (c 0.72, $CHCl_3$) R_f 0.27 (pentane-diethyl ether, 2:1); IR (film) ν 2986, 2935, 1642, 1298 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.10 (dd, J = 6,3 Hz, 1H), 4.98 (d, J = 6 Hz, 1H), 4.50 (m, 1H), 3.01 (s, 3H), 2.42 (m, 1H), 2.25 (m, 1H), 2.05 (m, 1H), 1.73 (m, 1H), 1.37 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.4, 139.2, 109.6, 73.0, 69.7, 44.0, 27.7, 26.1, 24.5, 20.6; HRMS-EI Calcd for $C_9H_{13}O_4S$: 217.0534; Found, 217.0541; Anal. calcd for $C_9H_{13}O_4S$ C, 51.71; H, 6.94; found C, 51.58; H, 6.99.



(1*S*,2*S*)-3,4-Dibromo-cyclohexa-3,5-diene-1,2-diol (59)

The biooxidation of *o*-dibromobenzene was performed according to the general procedure for large-scale fermentation. *o*-Dibromobenzene **311** (60 g) was added dropwise over 45 min to a 15- L fermentor containing a growing culture of *E. coli* JM 109 (pDTG601). After stirring the media for an additional 1 h, the cell broth was

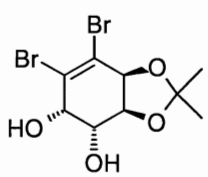
separated from the cells by centrifugation. The broth was extracted with 3 L of ethyl acetate using a rotary evaporator-driven continuous extractor over a three-day period. The combined organic layers were washed twice with approximately 10% by volume saturated sodium carbonate solution to remove any phenolic residue. The organic extracts of the fermentation broth were concentrated *in vacuo* and the dienediol precipitated by addition of pentane. Recrystallization from ethyl acetate/pentane provided the title compound as a white solid (32.8 g, 4.1 g/L): mp 144-146 °C (from ethyl acetate-pentane); $[\alpha^{22}_{D}]$ +104, (c 0.15, diethyl ether); R_f 0.36 (hexanes-ethyl acetate, 1:1); IR (film) ν 3175, 1621 cm^{-1}; ^1H NMR (300 MHz, acetone d_6) δ: 6.03 (dd, J = 9.9, 2.1 Hz, 1H), 6.00 (dd, J = 6.6, 2.4 Hz, 1H), 4.62 (d, J = 6.9 Hz, 1H), 4.55 (m, 1H), 4.28 (m, 2H); ^{13}C NMR (75 MHz, acetone d_6) δ: 133.4, 126.5, 126.2, 120.6, 74.2, 69.0; HRMS-EI calcd for $C_6H_6BrO_2$ (M^+): 267.8731, found: 267.8733; Anal calcd for $C_6H_6BrO_2$; C, 26.70; H, 2.24; Found C, 27.04; H, 2.32.



(3a*S*,7a*S*)-2,2-Dimethyl-4,5-dibromo-4,6-benzo[1,3]dioxole (315)

Diene diol **59** (3.0 g, 11.1 mmol, 1 equiv) was transferred to a 100-mL round-bottomed flask and suspended in 5 mL acetone and 15 mL of 2,2-DMP. A few crystals of *p*TsOH were added, and the reaction mixture was stirred at rt for 3 h. The reaction was quenched with 12 mL of 10% aq sodium hydroxide solution, and the acetone was removed under reduced pressure. The residue was diluted with ethyl acetate, and the layers were separated. The aqueous layer was then extracted with several portions of

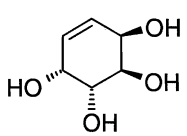
ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to provide a light oil (3.21 g, 95%), which was essentially pure. An analytical sample was obtained after chromatography over 10% deactivated silica gel, affording the title compound as a clear oil. $[\alpha]_D^{22}$ +101 (c 0.75, $CHCl_3$); R_f 0.50 (50% ethyl acetate in hexanes); IR (film) ν 2988, 2933, 2896, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, J = 9.9 Hz, 1H), 5.93 (dd, J = 9.9, 3.6 Hz, 1H), 4.82-4.72 (m, 2H), 1.45 (s, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ 128.7, 125.6, 123.8. 120.3, 106.9, 77.3, 71.3, 26.6, 25.0; HRMS-EI Calcd for $C_9H_{10}Br_2O_2$, 307.9047; Found, 307.9037.



(3a*S*,4*R*,5*S*,7a*S*)-2,2-Dimethyl-6,7-dibromo-4,5-dihydroxybenzo[1,3]dioxole (316)

The protected dienediol **315** (3.1 g, 10 mmol, 1 equiv) was suspended in 60 mL of 8:1 (by volume) mixture of acetone/ water. *N*-Methylmorpholine-*N*-oxide (2.34 g, 20 mmol, 2 equiv) was added followed by 4 crystals of osmium tetraoxide. The reaction mixture darkened slightly and was stirred for 18 h until consumption of starting material was complete as evidenced by TLC. The reaction mixture was quenched by addition of 5 mL sat aq sodium bisulfite, followed by a further addtition of 2 g solid sodium bisulfite, and the pH of the mixture was adjusted to approximately 2 by addition of conc HCl. The mixture was stirred for 15 min, and the acetone was removed under reduced pressure. The remaining aqueous portion was extracted repeatedly with ethyl acetate, and the

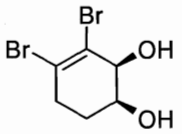
combined organic extracts were washed sequentially with 1N HCl, 20% aq solution of KOH, and brine before being dried over anhydrous $MgSO_4$. The organic solution was filtered through a short column of silica gel and the solvent evaporated to furnish 2.4 g of a white crystalline solid, 71% yield which required no further purification for the subsequent reaction. An analytical sample was obtained from a portion of the solid, recrystallized from ethyl acetate/ pentane. Mp 155/156 °C; $[\alpha]_D^{22}$ +5.47 (c 0.75, MeOH); R_f 0.3 (50% ethyl acetate in hexanes); IR (KBr) ν 3435, 3360, 2994, 2905, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 (dd, J = 1.2, 5.4 Hz, 1H), 4.50-4.45 (m, 2H), 4.34 (m, 1H), 2.68 (bs, 2H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.6, 125.6, 77.6, 75.3, 70.9, 69.1, 27.6, 26.1; HRMS-EI calcd for $C_8H_9O_4Br$, 326.8867; found, 326.8863; Anal Calcd for $C_9H_{12}Br_2O_4$: C, 31.42; H, 3.52, Found: C, 60.11; H, 7.78.



(-)-Conduritol E (60)

Dibromide **316** (0.50 g, 1.4 mmol, 1 equiv) was dissolved in 50 mL distilled THF and transferred to a flame-dried 100-mL round-bottomed flask equipped with a reflux condenser. The solution was degassed in an ultrasound bath and under positive argon pressure for 10 min. Azoisobutyronitrile (23 mg, 0.14 mmol, 0.1 equiv) was added, and the solution heated to steady reflux (83 °C external temp). At this time, tributyl tin hydride (1.0 mL, 3.36 mmol, 2 equiv) was added in a single portion. Reflux was maintained for 1.5 h until complete consumption of starting material was evidenced by TLC analysis. The reaction mixture was cooled, and potassium fluoride (2 g) was added. The resulting preciptitate was filtered, and the filtrate concentrated under reduced

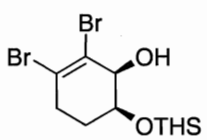
pressure. The residue was purified by flash column chromatography, eluting with 4:1 hexanes/ethyl acetate to 100% ethyl acetate to provide 170 mg (64%) of the de-brominated material. The solid was dissolved in 5 mL of methanol and to this solution was added 2 mL of a 3% (by volume) solution of conc HCl in methanol and the resulting solution stirred for 40 h after which time the solvent was removed under reduced pressure to provide a crude white solid. The solid was purified by flash column chromatography (4:1 chloroform/methanol) to give conduritol E as a white crystalline solid (78 mg, 81%). Mp 194/195 °C (lit[163] mp 193 °C); $[\alpha]_D^{20}$ -285 (c 1.0, H_2O), lit[163]: $[\alpha]_D^{20}$ -294 (c 1.0, H_2O) ; R_f 0.18 (chloroform-methanol, 4:1); IR (film) ν 3434, 1634 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 5.79 (d, J = 2.1 Hz, 2H), 4.27 (s, 2H), 3.93 (d, J = 0.9 Hz, 2H); ^{13}C NMR (75 MHz, MeOD) δ 130.7, 70.9, 67.6; HRMS-EI Calcd for $C_6H_{10}O_4$, 146.0579; Found, 146.0577.



(1*S*,2*S*)-3,4-Dibromo-cyclohexa-3-ene-1,2-diol (396)

Diol **5** (0.384g, 1.47 mmol, 1 equiv) was dissolved in 6 mL MeOH, and the round-bottomed flask containing the solution was subsequently placed into an ice/NaCl bath. Potasium azodicarboxylate (0.93g, 4.27 mmol, 3 equiv) was added in two portions to the methanolic solution. Acetic acid (0.85 mL, 12.78 mmol, 9 equiv) in 2 mL MeOH was added dropwise over 40 min. The reaction flask was allowed to warm to room temperature overnight (15 h). The reaction was quenched by adding 2 mL saturated Na_2CO_3 solution and stirring for 20 min. Methanol was removed under reduced pressure

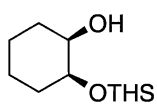
and the residue diluted with 10 mL EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and treated with activated charcoal. Filtration and subsequent concentration of the filtrate under reduced pressure afforded **318** as a white crystalline solid (0.367g, 95%). Mp 175-176 °C; $[\alpha]_D^{21}$ -50.4 (c 0.75, MeOH); R_f 0.23 (Hex: EtOAc, 1:1); IR (KBr pellet) ν 3246, 1626 cm^{-1}; ^1H NMR (300 MHz, acetone d_6) δ 4.61 (d, J = 6 Hz, 1H), 4.26 (s, 1H), 3.96-3.84 (m, 2H), 2.79-2.51 (m, 2H), 2.05-1.92 (m, 1H), 1.85-1.73 (m, 1H); ^{13}C NMR (75 MHz, acetone d_6) δ 127.1, 124.9, 73.5, 68.25, 35.2, 26.9; HRMS-EI Calcd for $C_6H_8Br_2O_2$, 271.8872; Found, 271.8871; Anal calcd for $C_6H_8Br_2O_2$; C, 26.50; H, 2.97; Found C, 27.34; H, 3.16



(1*S*,2*S*)-1-[(Hexyldimethylsilyl)oxy]-3,4-dibromocyclohexa-3-ene-2-ol (397)

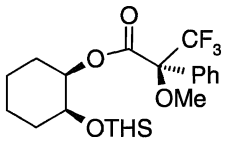
A 5-mL round-bottom flask was charged with diol **396** (200 mg, 0.74 mmol, 1 equiv), imidazole (65 mg, 0.96 mmol, 1.3 equiv) and 1 mL anhydrous DMF. The flask was cooled externally to -30 °C, then hexyldimethylsilyl chloride (0.15 mL, 0.78 mmol, 1.05 equiv) was added. The mixture was stirred at -30 °C for 1 h then placed in a freezer (-18 °C) for 21 h. The mixture was allowed to warm to room temperature and diluted with 50 mL ether, washed with 10 x1 mL distilled H_2O, brine, and then dried over $MgSO_4$. After filtration the filtrated was concentrated under reduced pressure. The crude silyl ether was purified by flash column chromatography (pentane: Et_2O, 10:1) to give **397** as a clear and colorless oil (0.26 g, 86%). $[\alpha]_D^{21}$ -41.1 (c 0.75, MeOH); R_f 0.23 (Pentane: Et_2O, 10:1);

IR (film) ν 3547, 2958, 2868, 1628 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.26-4.17 (m, 1H), 4.03-3.93 (m, 1H), 2.84 (d, *J* = 4, 1H), 2.77-2.64 (m, 1H), 2.63-2.48 (m, 1H), 2.10-1.9 (m, 1H), 1.77-1.57 (m, 2H), 0.95-0.84 (m, 13H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.8, 127.8, 122.9, 74.1, 73.6, 69.6, 35.1, 34.1, 27.2, 24.8, 20.2, 20.0, 18.5, 18.4; HRMS-EI Calcd for $C_{14}H_{26}Br_2O_2Si$, 328.9032; Found,328.9026; Anal calcd for $C_{14}H_{26}Br_2O_2Si$; C, 40.59; H, 6.33; Found C, 40.96; H, 6.36.



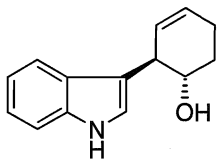
(1*R*, 2*S*)-2-[(Hexyldimethylsilyl)oxy]cyclohexan-1-ol (360)

A flask containing a magnetic stirring bar was charged with dibromide **397** (0.219 g, 0.53 mmol, 1 equiv), triethylamine (0.5 mL, 3.56 mmol, 7 equiv), platinum oxide (Adam's catalyst, 24 mg, 0.11 mmol, 0.2 equiv) and 0.5 mL MeOH. The reaction flask was evacuated, flushed with hydrogen via a filled balloon (1 atm), and stirred until total consumption of starting material was observed by TLC (6h). The crude mixture was filtered through a short plug of Celite, and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (pentane/ Et_2O, 10:1) to give the title compound as a clear and colorless oil (71 mg, 52%) having spectral data matching that of previously reported. $[\alpha]_D^{23}$ + 3.4 (c 1.0, $CHCl_3$); lit[136]: $[\alpha]_D^{23}$ + 3.3 (c 1.0, $CHCl_3$).



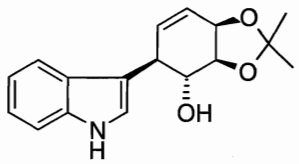
Mosher ester derivative 361.

Alcohol **360** (20 mg, 0.076 mmol, 1 equiv) was transferred to a flame-dried round-bottomed flask containing magnetic stirring bar under argon atmosphere. Anhydrous triethylamine (17μL) was added followed by DMAP (4.8mg, 0.038mmol, 0.5 equiv). (*R*)-(-)-α-Methoxy-α-trifluoromethyl-phenylacetic acid chloride (23μL, 0.11 mmol, 1.5 equiv) was added dropwise. Within minutes a white precipitate was observed. The reaction was stirred overnight. The reaction mixture was then diluted with 5 mL methylene chloride, transferred to a separatory funnel and washed with 5 mL saturated solution of sodium bicarbonate. The layers were separated and the organic layer dried ($MgSO_4$) and the solvent evaporated to provide the ester as a crude oil. The ester was purified by flash column chromatography (pentane: Et_2O, 10:1) to afford the ester as a clear and colorless oil (20 mg, 57%). R_f 0.46 (pentane: Et_2O, 10:1); IR (film) 2948, 2867, 1745, 1463, 1450, 1379, 1263, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ: 7.60 (m, 2 H), 7.40 (m, 3 H), 5.12 (m, 1H) 3.80 (m, 1H), 3.55 (m, 3H), 1.75-1.55 (m, 7H), 1.5-1.2 (m, 2H) 0.88 (dd, J = 6.8, 5.2 Hz, 6 H), 0.81 (d, J = 4.1 Hz, 6H), 0 (s, 3 H), -0.10 (s, 3 H) ^{19}F NMR (188 MHz, $CDCl_3$) δ: -72.4 ppm. Lit:[136] ^{19}F NMR (188 MHz, $CDCl_3$) δ: -72.8 ppm.



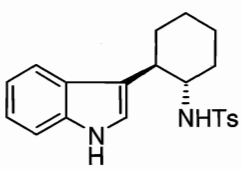
2-(1*H*-Indol-3-yl)-cyclohex-3-enol (404).

Indole (367 mg, 3.12 mmol, 3 eq.) and vinyl epoxide **405** (100 mg, 1.04 mmol, 1.0 eq.) were heated on a previously-activated silica-gel surface (1.0 g) at 70 °C for 27 hours as described in the general procedure. The silica gel supporting the reaction mixture was cooled to rt and chromatographed directly on flash silica (hexanes/ethyl acetate; gradient elution, 4:1 to 1:1), providing the title compound as an off-white crystalline solid (68 mg, 32%); The crystalline material was recrystallized from methylene chloride/pentane. R_f 0.5 (hexanes-ethyl acetate, 1:1); mp (sealed tube) 121-122 °C; IR (film) ν 3543, 3410, 3056, 3022, 2922, 1618, 1456, 1433, 1339, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.03 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.15 (m, 1H), 7.00 (m, 2H), 5.77 (m, 1H), 5.66 (dd, J = 9.7, 1.2 Hz, 1H), 3.91 (ddd, J = 10.3, 7.3, 2.9 Hz, 1H), 3.48, (m, 1H), 2.2 (m, 2H), 1.98 (m, 1H), 1.84 (bs, 1H), 1.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.3, 129.0, 127.4, 127.0, 122.9, 122.6, 120.0, 119.8, 117.2, 111.7, 72.3, 43.4, 29.4, 24.8; HRMS-EI Calcd for $C_{14}H_{15}NO$ 213.1153, Found: 213.1148.



5-(1*H*-Indol-3-yl)-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-ol (407).

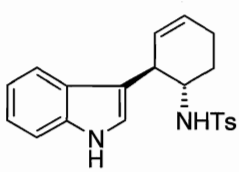
Indole (211 mg, 1.8 mmol, 3 eq.) and vinyl epoxide **406** (100 mg, 0.60 mmol, 1.0 eq.) were heated at 70 °C on a previously-activated silica-gel surface (600 mg) for 20 hours as described in the general procedure. The reaction mixture on silica gel was purified by chromatography on flash silica gel (hexanes/ethyl acetate; gradient elution, 4:1 to 1:1), providing a foamy solid (86 mg, 51%); R_f 0.28 (pentane/ethyl acetate, 1:1); $[\alpha]_D^{28}$ +35.45; (c 0.35, MeOH); IR (film) ν 3407, 2927, 1456, 1379 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.12 (m, 1H), 7.05-6.95 (m, 2H), 5.93 (s, 2H), 4.66 (d, J = 6.2 Hz, 1H), 4.12 (m, 1H), 3.80 (t, J = 9.3 Hz, 1H), 3.45 (d, J = 9.8 Hz, 1H), 2.21 (bs, 1H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.0, 135.6, 126.8, 123.9, 123.2, 122.7, 119.9, 119.8, 114.5, 111.0, 79.4, 74.0, 73.2, 40.9, 28.7, 26.2; HRMS-EI Calcd for $C_{17}H_{19}NO_3$ 285.1364, Found 285.1364; Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 70.25; H, 7.03.



***N*-[2-(1*H*-Indol-3-yl)-cyclohexyl]-4-methyl-benzenesulfonamide (409).**

Indole (95 mg, 0.81 mmol, 3 eq.) and *N*-tosylaziridine **408** (68 mg, 0.27 mmol, 1.0 eq.) were heated on a previously-activated silica-gel surface (800 mg) at 70 °C for 22 hours according to the general procedure. The silica gel supporting adsorbed reaction mixture

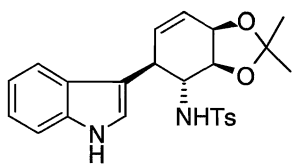
was loaded onto a flash silica column and eluted with hexanes/ethyl acetate; (4:1 to 2:1) to give the title compound as a white foam (38 mg, 38%); R_f 0.22 (hexanes/ethyl acetate, 2:1); IR (film) ν 3404, 2930, 1598, 1457, 1316, 1157, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.27 (m, 2H), 7.16 (m, 3H), 6.90 (m, 3H), 6.75 (d, J = 2.5 Hz, 1H), 4.51 (d, J = 3.3 Hz, 1H), 3.17 (m, 1H), 2.65 (dt, J = 11.2, 3.5 Hz, 1 H), 2.50 (m, 1H), 2.33 (s, 3H), 1.95 (m, 1H), 1.75 (m, 3H), 1.25 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.0, 136.9, 136.5, 129.4, 126.9, 126.4, 122.2, 122.1, 119.4, 116.7, 111.7, 57.5, 42.0, 35.1, 33.7, 26.4, 25.3, 21.8; HRMS-EI Calcd for $C_{21}H_{24}N_2O_2S$ 368.1558, Found 368.1553; Anal. Calcd for $C_{21}H_{24}N_2O_2S \cdot H_2O$: C, 65.26; H, 6.25. Found: C, 65.88; H, 6.44.



***N*-[2-(1*H*-Indol-3-yl)-cyclohex-3-enyl]-4-methyl-benzenesulfonamide (411).**

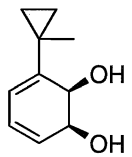
Indole (141 mg, 1.2 mmol, 3 eq.) and vinyl aziridine **410** (100 mg, 0.40 mmol, 1.0 eq.) were heated on a previously-activated silica-gel surface (1.0 g) at 70 °C for 20 hours as described in the general procedure. The silica gel supporting the starting materials was directly loaded onto a flash silica gel column and the product purified by flash chromatography (hexanes/ethyl acetate; gradient elution, 4:1 to 2:1), providing the tosyl derivative **411** as an off-white solid (112 mg, 76%). R_f 0.2 (pentane/ethyl acetate, 3:1); mp 158-160 °C; IR (film) ν 3406, 3285, 3027, 2924,2860, 1598, 1493, 1457, 1420, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.35-7.20 (m, 2 H), 7.17-7.10 (m, 2H), 7.0 (d, J = 8.0 Hz, 2H), 6.97 (m, 1H), 6.82 (s, 2H), 5.88 (m, 1H), 5.65 (d, J = 9.5 Hz, 1H), 4.85 (d, J = 5.3 Hz, 1H), 3.50 (s, 2H), 2.33 (s, 3H), 2.20 (s, 2H),

2.05-1.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.3, 137.1, 137.0, 129.7, 128.1, 127.6, 127.2, 123.3, 122.4, 119.7, 119.4, 166.5, 111.5, 53.4, 39.9, 26.3, 22.8, 21.9; HRMS-EI Calcd for $C_{21}H_{22}N_2O_2S$ 366.1401, Found 366.1398; Anal. calcd for $C_{12}H_{22}N_2O_2S$: C, 68.83; H, 6.05. Found: C, 68.14; H, 6.07.



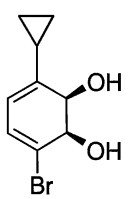
3-Indolyl-1-*H*-3-(2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxolyl-4-tosylamine (412).

Indole (73 mg, 0.621 mmol, 2.0 eq.) and vinyl aziridine **402** (100 mg, 0.311 mmol, 1.0 equiv) were allowed to react on a previously-activated silica-gel surface (1.0 g) at 70 °C for 17 hours as described in the general procedure. The silica gel supporting adsorbed reaction mixture was loaded onto a flash silica column and eluted with hexanes/ethyl acetate; 4:1 to 2:1, to give the title compound as a brown crystalline solid (130 mg, 48%); R_f 0.26 (hexanes/ethyl acetate, 1:1); $[\alpha]_D^{19}$ +59 (c 0.99, $CHCl_3$); IR (film) ν 3389, 3039, 2985, 2931, 1718, 1621, 1599, 1458, 1375, 1246, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.30-7.15 (m, 4H), 7.10 (m, 1H), 6.97 (m, 2 H), 6.83 (d, J = 7.5 Hz, 2 H), 5.93 (s, 2H), 5.12 (d, J = 7.3 Hz, 1H), 4.65 (m, 1H), 4.19 (m, 1H), 3.75 (dd, J = 17, 8.4 Hz, 1H), 3.49 (d, J = 9.8 Hz, 1H), 2.26 (s, 3H), 1.51 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.3, 138.3, 136.8, 135.9, 129.0, 126.8, 126.6, 123.6, 123.5, 122.2, 119.7, 119.3, 114.1, 110.1, 72.7, 57.5, 39.4, 28.4, 26.4, 21.8; HRMS-EI Calcd for $C_{24}H_{26}N_2O_4S$ 438.16158, Found 438.16114; Anal Calcd for $C_{24}H_{26}N_2O_4S \cdot H_2O$: C, 63.14; H, 6.18. Found: C, 63.32; H, 5.95.



(1*S*,2*R*)-3-(1-Methyl-cyclopropyl)-cyclohexa-3,5-diene-1,2-diol (431)

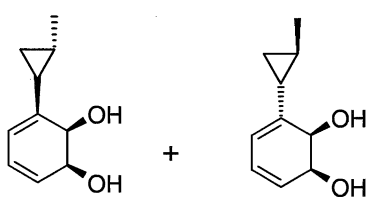
The diol was isolated from a crude mixture from biotransformation of the corresponding cyclopropylbenzene by *E. coli* JM 109 (pDTG601) according to the general procedure for shake-flask fermentation. After purification by flash silica gel chromatography (hexanes-ethyl acetate, 2:1; 10% deactivated silica), the *cis*-dienediol was recrystallized from ethyl acetate/ pentane to afford the *cis*-dihydroarene diol as a white crystalline solid, 56 mg/L; mp 81-81.5 °C; $[\alpha]_D^{26}$ +65.5, (c 1.0, MeOH); R_f 0.30 (hexanes-ethyl acetate, 1:1); IR (film) ν 3290, 1639, 1582, 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.90 (d, J = 5.6 Hz, 1 H), 5.85 (d, J = 6.0 Hz, 1 H), 5.63 (d, J = 9.0 Hz, 1 H), 4.32 (s, 1 H), 4.10 (dd, J = 14, 10 Hz, 1 H), 3.72 (d, J = 5.0 Hz, 1H), 1.23 (s, 3 H), 0.92 (m, 2 H), 0.56 (m, 2H); HRMS-EI calcd for $C_{10}H_{14}O_2$, 166.0994; found, 166.0995



(1*R*,2*R*)-3-Bromo-6-cyclopropyl-cyclohexa-3,5-diene-1,2-diol (433)

The diol was isolated from a crude mixture from biotransformation of the corresponding cyclopropylbenzene by *E. coli* JM 109 (pDTG601) according to the general procedure for

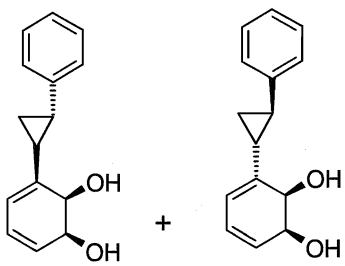
shake-flask fermentation. Purification by flash silica gel chromatography (hexanes-ethyl acetate, 3:2; 10% deactivated silica) furnished the *cis*-dihydroarene diol as a white crystalline solid, 32 mg/L; $[\alpha]_D^{26}$ -17.5, (c 0.65, $CHCl_3$); R_f 0.76 (hexanes-ethyl acetate, 1:1); IR (film) ν 3290, 1631, 1550 cm^{-1}; ^1H NMR (300 MHz, acetone d_6) δ: 6.27 (d, J = 6.3 Hz, 1 H), 5.47 (d, J = 6.3 Hz, 1 H), 5.63 (d, J = 9 Hz, 1 H), 4.23 (d, J = 2.4 Hz, 2 H), 4.18 (m, 1 H), 3.92 (d, J = 7.5 Hz, 1H), 2.88 (s, 1H), 1.65 (m, 1H), 0.76 (m, 2H), 0.60 (m, 2H); ^{13}C NMR (75 MHz, acetone d_6) δ: 144.2, 126.6, 124.2, 115.6, 72.6, 70.3, 13.2, 6.4, 6.0.



(1*S*,2*R*)-3-(2-Methyl-1-cyclopropyl)-cyclohexa-3,5-diene-1,2-diol (435a, 435b)
1:1 mixture of diastereoisomers.

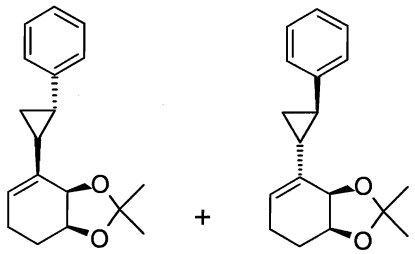
The crude mixture of diols was isolated from fermentation with *Escherichia coli* JM 109 (pDTG601) according to the general procedure for shake-flask fermentation. The products were purified by flash column chromatography on 10% deactivated silica gel (hexanes-ethyl acetate, 1:1) to provide the crystalline diols **435a** and **435b** as an inseparable mixture of diastereoisomers, (90 mg/L). Mp 42-46 °C; $[\alpha]_D^{22}$ +71.3 (c 0.5, $CHCl_3$); R_f 0.3 (hexanes-ethyl acetate, 1:1); IR (film) ν 3350, 2951, 1585, 1384, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.62 (d, J = 9.8 Hz, 1H), 5.55 (m, 1H), 4.25 (s, 1H), 3.78 (s, 1H), 2.30 (bs, 1H), 1.87 (bs, 1H), 1.20 (m, 1H), 1.05 (d , J = 2.8 Hz, 3 H), 0.97 (m, 1H), 0.65, (m, 1H), 0.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.5,

128.0, 127.9, 124.9, 124.8, 120.7, 117.4, 117.3, 70.3, 70.2, 69.6.6, 69.5, 23.4, 23.3, 19.2, 16.4, 16.0, 15.2, 14.6, 14.5; HRMS-EI calcd for $C_{10}H_{14}O_2$ (M^+), 166.0993; found, 166.0994.



(1*S*,2*R*)-3-(2-Phenyl-cyclopropyl)-cyclohexa-3,5-diene-1,2-diol (438a, 438b)
1:1 mixture of diastereoisomers.

The crude mixture of diols was isolated from fermentation with *Escherichia coli* JM 109 (pDTG601) according to the general procedure for shake-flask fermentation. The products were purified by flash column chromatography on 10% deactivated silica gel (hexanes-ethyl acetate, 1:1) to provide the title compound as a clear oil, which was an inseparable mixture of diastereoisomers, (140 mg/L): $[\alpha]_D^{22}$ +38.6 (c 0.89, $CHCl_3$); R_f 0.28 (hexanes-ethyl acetate, 1:1); IR (film) ν 3346, 2922, 1603, 1498, 1403 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.19 (m, 2H), 7.13-7.01 (m, 3H), 5.86 (m, 1H), 5.67-5.60 (m, 2H), 4.27 (s, 1H), 3.87 (d, J = 5.8 Hz, 1H), 2.58-2.41 (bs, 1H), 2.07 (m, 1H), 1.81-1.71 (m, 1H), 1.33 (m, 1H), 1.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ:142.4, 142.3, 142.1, 142.0, 128.9, 128.8, 128.6, 128.5, 128.2, 126.4, 126.3, 126.2, 126.2, 124.8, 124.7, 120.9, 118.5, 118.3, 70.3, 70.1, 69.4, 27.1, 26.9, 26.5, 25.5, 25.3, 16.9, 16.2, 15.7; HRMS-EI calcd for $C_{15}H_{16}O_2$ (M^+): 228.1150; found, 228.1139.

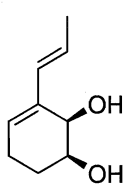


3(*R*),7(*S*)-2,2-Dimethyl-7-(2-phenylcyclopropyl)-3a,4,5,7a-tetrahydrobenzo[1,3]dioxole (442)
1:1 mixture of diastereoisomers

A mixture of diene diols **438a** and **438b** (140 mg, 0.61 mmol, 1 equiv) was dissolved in 5 mL methanol, and the solution transferred to a 25-mL round-bottomed flask equipped with magnetic stirring bar and addition funnel. The flask was cooled externally to 0 °C at which time PAD reagent (331 mg, 1.71 mmol, 2.8 equiv) was added to the reaction flask. The yellow slurry was stirred for 10 min, then the addition funnel was charged with acetic acid (236 μL, 3.99 mmol, 6.5 equiv) dissolved in 5 mL methanol. The acetic acid solution was added dropwise over a 1 h period and the yellow slurry was allowed to warm to rt overnight. A saturated solution of sodium bicarbonate was used to adjust the pH to approximately 8.5 and the reaction mixture was diluted with 20 mL ethyl acetate. The layers were separated and the aqueous layer extracted with 3 portions of ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and the drying agent removed by filtration. The solvent was removed under reduced pressure to provide 125 mg crude product which was used directly in the subsequent reaction without further purification.

The crude product from diimide reduction was dissolved in a minimum amount of acetone and transferred to a 25 mL round-bottomed flask equipped with magnetic stirring bar. 2,2-DMP (471 μL, 3.9 mmol, 6.4 equiv) was added as a neat solution followed by

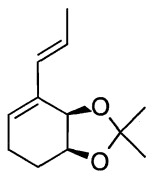
several crystals of *p*TsOH. The reaction mixture was stirred for 1.5 h at which time the solvent was removed under vacuum. The residue was purified by flash column chromatography (hexanes-ethyl acetate, 3:1), affording the title compound, which was as a clear and colorless oil, as an inseparable mixture of diastereoisomers, (66 mg, 40% yield over 2-steps); $[\alpha]_D^{22}$ +30.2 (c 1.0, $CHCl_3$); R_f 0.55 (hexanes-ethyl acetate, 5:1); IR (film) ν 2984, 2931, 1604, 1498, 1455, 1367, 1241 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.16 (m, 2H), 7.05 (m, 3H), 5.72/5.50 (t, *J* = 3.8 Hz, 1H), 4.35 (m, 1H), 4.25 (m, 1H), 2.20-2.05 (m, 1H), 2.05 (m, 1H), 1.90-1.75 (m, 2 H), 1.70-1.60 (m, 1H), 1.35 (d, *J* = 3.5 Hz, 3H), 1.30 (d, *J* = 3.2 Hz, 3H), 1.22 (m, 1H), 1.05 (m, 2 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.0, 141.9, 135.3, 135.1, 127.5, 127.2, 124.9, 124.7, 124.4, 124.4, 123.0, 122.0, 119.4, 107.3, 73.3, 72.9, 72.4, 27.0, 26.9, 25.7, 25.7, 25.5, 24.5, 24.1, 22.5, 19.6, 19.5, 14.2, 14.0; HRMS-EI calcd for $C_{18}H_{22}O_2$ (M^+): 270.1619; found, 270.1603; Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.56; H, 8.20, Found, C, 79.23; H, 8.15.



(1*S*,2*R*)-3-Prop-1-enyl-cyclohex-3-ene-1,2-diol

To a solution of dienediol **454** (1.35 g, 8.8 mmol, 1.0 equiv) in 20 mL MeOH at 0 °C was added portionwise PAD reagent (5.16 g, 26.6 mmol, 3 equiv) over 10 min. The yellow slurry was stirred for 10 min before addition of AcOH (3.55 mL, 61.6 mmol, 7 equiv) in 20 mL MeOH over a 1 hour period. The reaction mixture was stirred overnight, warming slowly to rt over 12 h. The reaction mixture was quenched by addition of 12

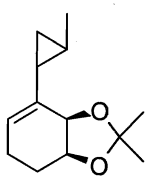
mL saturated solution of sodium carbonate. MeOH was removed under vacuum and the residue diluted with ethyl acetate. The layers were separated and the aqueous portion extracted 3 times with 15 mL ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Removal of of the drying agent by filtration and evaporation of the solvent under reduced pressure provided a solid which was recrystallized to give 828 mg of the title compound as a tan solid (61%). Mp 107-108 °C (from methylene chloride-pentane); $[\alpha]_D^{24}$ -133 (c 0.5, $CHCl_3$); R_f 0.21 (hexanes-ethyl acetate, 1:1); IR (film) ν 3260, 2945, 2871, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (d, J = 16 Hz, 1H), 5.84 (m, 1H), 5.63 (t, J = 3.9 Hz, 1H), 4.30 (d, J = 3.6 Hz, 1H), 3.63 (m, 1H), 2.23 (bs, 2H), 2.15 (m, 2H), 1.72 (d, J = 5.9 Hz, 3H), 1.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.9, 131.5, 128.9, 123.7, 69.7, 65.9, 25.3, 25.1, 18.3; HRMS-EI calcd for $C_9H_{14}O_2$ (M^+): 154.0993; found, 154.0994.



3(*S*),7(*R*)-2,2-Dimethyl-propenyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxole (455)

The diol derived from diimide reduction of trienediol **454** (828 mg, 5.37 mmol, 1 equiv) was transferred to a 50-mL round-bottomed flask and dissolved in 5 mL acetone. 2,2-DMP (1.2 mL, 10.1 mmol, 1.9 equiv) was added followed by 1 spatula tip of *p*TsOH. The solution was stirred at rt for 2.5 h before the reaction was quenched with 10 mL of saturated sodium carbonate solution, and the acetone removed under reduced pressure. The cloudy mixture was diluted with 15 mL ethyl acetate and 2 mL of distilled water.

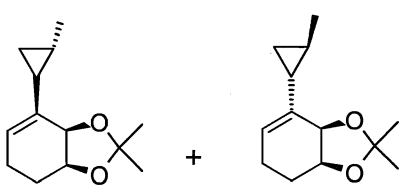
The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to provide a tan oil, purified by flash column chromatography (98:2 hexanes-ethyl acetate) to afford the title compound as a clear and colorless oil, 900 mg (86%): $[\alpha]_D^{24}$ +68.1 (c 0.72, $CHCl_3$); R_f 0.56 (10% ethyl acetate in hexanes); IR (neat) ν 2984, 2932, 1451, 1367 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (d, J = 15.9 Hz, 1H), 5.83 (m, 1H), 5.73 (t, J = 4.2 Hz, 1H), 4.58 (d, J = 6.0 Hz, 1H), 4.22 (m, 1H), 2.15 (m, 1H), 1.96 (m, 1H), 1.71 (d, J = 6.3 Hz, 3 H), 1.69 (m, 2H), 1.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.3, 131.9, 129.3, 124.5, 108.3, 73.6, 71.4, 28.1, 26.3, 26.1, 21.6, 18.4; HRMS-EI Calcd for $C_{12}H_{18}O_2$, 194.1306; found, 194.1304 .



3(*R*),7(*S*)-2,2-Dimethyl-(2-methylcyclopropyl)-3a,4,5,7a-tetrahydro-benzo[1,3]dioxle (456)

To a solution of diethyl zinc (16.5 mL of 1.0 M solution in hexanes, 16.5 mmol, 4 equiv) in 16 mL anhydrous methylene chloride at 0 °C was added freshly distilled trifluoroacetic acid (0.65 mL, 8.25 mmol, 2 equiv) in 8 mL methylene chloride *very slowly* (*ca.* 20 min). The thick, white slurry was stirred at 0 °C for 20 min at which time diiodomethane (0.66 mL, 8.25 mmol, 2 equiv) in 8 mL was introduced to the reaction flask by cannulation. The resulting gray slurry was stirred for 20 min before addition of propenyl protected diol **455** (800 mg, 4.06 mmol, 1 equiv) dissolved in 8 mL methylene chloride. The reaction flask was removed from the ice bath and the slurry allowed to warm to rt over 30 min.

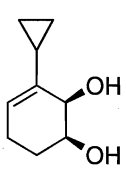
Progress of the reaction was monitored by TLC (10% ethyl acetate in hexanes, $KMnO_4$ stain). When deemed complete, the reaction was quenched by addition of 20 mL saturated solution of NH_4Cl and the layers were separated. The aqueous layer was extracted with 2 portions of methylene chloride and the combined organic layers dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure provided an oil, which was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford the corresponding cyclopropane as a clear and colorless oil, (567 mg, 67%). $[\alpha]_D^{24}$ +64.3 (c 0.4, $CHCl_3$); R_f 0.44 (hexanes-ethyl acetate, 9:1); ^1H NMR (300 MHz, $CDCl_3$) δ: 5.32 (m, 1H), 4.17 (m, 1H), 4.15 (m, 1H), 1.98 (s, 1H), 1.73 (m, 2H), 1.27 (m, 6H), 0.94 (m, 4H), 0.85 (2H), 0.42 (m, 1H), 0.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.1, 122.4, 108.2, 74.2, 73.6, 28.0, 26.5, 25.7, 23.1, 20.7, 18.9, 14.2, 13.4 ppm (single diastereomer).



3(*R*),7(*S*)-2,2-Dimethyl-7-(2-methyl-cyclopropyl)-3a,4,5,7a-tetrahydro-benzo[1,3]dioxole (456)
1:1 mixture of diastereoisomers

A mixture of reduced diols **435a** and **435b** (40 mg, 0.24 mmol, 1 equiv) were transferred to a 10-mL round-bottomed flask and dissolved in 2 mL acetone. 2,2-DMP (250 μL, 2.4 mmol, 10 equiv) was added followed by 1 crystal *p*TsOH. The solution was stirred at rt for 24 hours before the reaction was quenched with 1 mL of saturated sodium bicarbonate solution. The cloudy mixture was diluted with 15 mL ethyl acetate and 2 mL of distilled

water. The layers were separated and the aqueous layer back-extracted with fresh ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to provide a tan oil (24 mg) which was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford the title compound as a clear oil and inseparable mixture of diastereoisomers, 16 mg (23%): $[\alpha]_D^{22}$ +47.5 (c 0.4, $CHCl_3$); R_f 0.44 (10% ethyl acetate in hexanes); IR (film) ν 3353, 2984, 2930, 1430, 1366 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.43/5.37 (t, J = 3.8 Hz, 1H), 4.47 (m, 1H), 4.17 (m, 1H), 2.15-2.00 (m, 1H), 1.85-1.70 (m, 2H), 1.65-1.50 (m, 2H), 1.34 (d, J = 6 Hz, 1H), 1.03 (d, J = 5.8 Hz, 2H), 0.9-0.75 (m, 1H), 0.68 (m, 1H) 0.51 (dd, J = 8.9, 4.8 Hz, 1H, 0.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 122.8, 122.5, 108.5, 74.8, 74.6, 73.9, 28.3, 26.9, 26.1, 23.5, 23.4, 21.1, 21.0, 19.6, 19.2, 15.2, 14.5, 13.8, 13.6; HRMS-EI calcd for $C_{13}H_{20}O_2$, 208.1463; found, 208.1468.

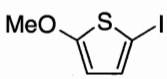


(1*S*,2*R*)-3-Cyclopropyl-cyclohexa-3-ene-1,2-diol (457)

From (1*R*,2*R*)-3-Bromo-6-cyclopropyl-cyclohexa-3,5-diene-1,2-diol **433**

Diol **433** (100 mg, 0.43 mmol, 1 equiv) was dissolved in 4 mL MeOH and transferred to a thick-walled hydrogenation flask. Distilled triethylamine (62 μL, 0.43 mmol, 1 equiv) was added followed by PtO_2 (Adams' catalyst, 19 mg, 0.087 mmol, 20 mol %). The flask was placed on a Parr hydrogenation apparatus, evacuated, and the headspace replaced with hydrogen gas (3 atm). The flask was allowed to shake at rt for a period of

1.5 hr. The reaction mixture was filtered through Celite and washed with several portions of methanol, concentrated, and purified by flash column chromatography, (hexanes-ethyl acetate, 3:2) and the solvent removed under reduced pressure to provide the title compound as an oily solid, (27 mg, 41%). Spectral data are consistent with that of the same compound prepared by enzymatic oxidation from cyclopropyl benzene and subsequent diimide reduction. R_f 0.27 (hexanes-ethyl acetate, 1:1); $[\alpha]_D^{26}$ -33 (c 1.0, MeOH), $[\alpha]_D^{23}$ -126 (c 1.0, MeOH). 26% optical purity.

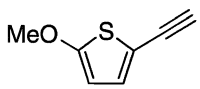


2-Iodo- 5-methoxythiophene (13).[200]

A flame-dried 100 mL round-bottomed flask was charged with 2-bromo-5-methoxythiophene (0.5 g, 2.5 mmol, 1.0 equiv) dissolved in 32 mL anhydrous THF. The flask was cooled to -60 °C by submersion in a liquid nitrogen/acetone slurry. The solution was then treated with *n*BuLi (1.75 mL of 1.6 M solution in hexanes, 2.8 mmol, 1.1 equiv), added over several minutes. The end of the addition was accompanied by a color change from colorless to bright yellow. The solution was maintained at -60 °C for an additional half hour at which time a solution of iodine (710 mg, 2.8 mmol, 1.1 equiv) in 3 mL THF at rt was added via cannula to the yellow solution of lithiated thiophene. The reaction was allowed to warm to 0 °C over 2 h and quenched with a solution of 10% aq $Na_2S_2O_3$. The reaction mixture was diluted with 25 mL of diethyl ether and the biphasic mixture transferred to a separatory funnel. The layers were separated and the aqueous layer extracted with diethyl ether (2 x 10 mL). The combined organic extracts

were washed with brine and dried over anhydrous $MgSO_4$. The crude product was filtered through a short plug of silica, and the solvent removed under reduced pressure to provide the title compound as a pale yellow oil, 277 mg, 76%.[201]

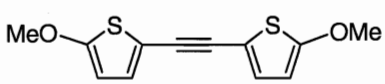
R_f 0.57 (5% ethyl acetate in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, J = 4.1 Hz, 1H), 5.85 (d, J = 4.0 Hz, 1H), 3.77 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 140.3, 134.8, 106.1, 60.8.



2-Methoxy-5-ethynylthiophene (482).

2-Iodo-5-methoxythiophene **13** (3.0 g, 12.5 mmol, 1.0 equiv) was dissolved in 45 mL freshly distilled triethylamine and cooled to 0° C. TMS-acetylene (1.38 mL, 13.75 mmol, 1.1 equiv) was added via syringe, followed by cuprous iodide (95 mg, 0.5 mmol, 0.04 equiv), and *bis*-(triphenylphosphino) palladium (II) dichloride (176 mg, 0.25 mmol, 0.02 equiv). The reaction was stirred 40 h at rt, during which time an orange precipitate formed. The salts were removed by filtration on a Büchner funnel and the reaction mixture diluted with 50 mL diethyl ether. The layers were separated and the organic phase washed twice with 30 mL sat. solution of ammonium chloride. The aqueous layers were combined and extracted twice with 15 mL diethyl ether. The ethereal extracts were combined, washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent was removed under reduced pressure to provide an orange oil (2.8 g) which was dissolved in 30 mL of THF and treated with tetrabutyl ammonium fluoride (5.9 g, 18.7 mmol, 1.5 equiv). After 1 h, the reaction mixture was treated with 20 mL sa. solution of ammonium chloride, 10 mL water, and 30 mL diethyl

ether. The mixture was transferred to a separatory funnel and the aqueous layer separated from the organic layer. The aqueous phase was extracted three times with 10 mL portions of diethyl ether. The organic layers were combined, washed with brine, and dried over $MgSO_4$. The solvent was removed *in vacuo* to provide a crude brown resin which was distilled under vacuum (0.3 mm Hg/ 90 °C), affording 1.1g of the alkyne (65%) as a pale yellow oil which darkened when exposed to air: R_f 0.32 (5% ethyl acetate in hexanes); IR (neat) ν 3306, 2253, 1543, 1482, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (d, J = 4.1 Hz, 1H), 5.87 (d, J = 4.3 Hz, 1H), 3.72 (s, 3H), 2.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 132.2, 108.5, 104.1, 79.4, 78.0, 60.6; HRMS-EI Calcd for C_7H_6OS 138.0139; Found 138.0135.

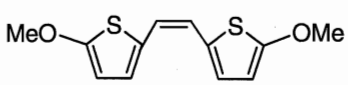


[*bis*-(5-Methoxy)-2-thienyl]acetylene (12).

2-[(5-Methoxy)-thienyl]acetylene **482** (0.92 g, 6.66 mmol, 1.0 equiv) and 2-iodo-5-methoxythiophene **13** (1.6 g, 6.66 mmol, 1.0 equiv) were dissolved in 90 mL anhydrous THF. To this solution was added cuprous iodide (25 mg, 0.13 mmol, 0.02 equiv), *bis*-(triphenylphosphino) palladium (II) dichloride (93 mg, 0.13 mmol, 0.02 equiv), and diisopropylamine (1.4 mL, 10 mmol, 1.5 equiv). The suspension was stirred and degassed using a stream of argon pressure for 15 minutes. After removal of the argon stream, the reaction mixture stirred for 14 h at rt at which time the reaction mixture was treated with 5 mL saturated solution of ammonium chloride and diluted with 30 mL of water and 100 mL of diethyl ether. The biphasic mixture was introduced into a separatory funnel and the layers separated. The aqueous phase was extracted twice with

ether and the ethereal extracts combined, washed with brine and dried over anhydrous $MgSO_4$. Removal of the drying agent by filtration and evaporation of the solvent provided a dark brown oil which was purified by flash column chromatography (5% ethyl acetate in hexanes) affording the title compound as a yellow crystalline solid, 600 mg, 36% yield. Additionally, 2-iodo-5 methoxythiophene was recovered (800 mg).

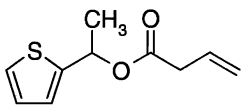
R_f 0.2 (5% ethyl acetate in hexanes); Mp 80/82 °C; IR (film) ν 2937, 1557, 1502, 1424 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J = 3.8 Hz, 1H), 6.10 (d, J = 4.1 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 131.2, 109.3, 104.4, 84.9, 60.5; HRMS-EI Calcd for $C_{12}H_{10}O_2S_2$, 250.0122, Found, 250.0125; Anal. Calcd for $C_{12}H_{10}O_2S_2$: C, 57.58; H, 4.03; Found: C, 57.24; H, 3.81.



***cis-bis*- 2-(2-Methoxy-5-thienyl)-ethylene (489).**

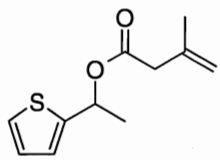
Thiophene dimer **12** (60 mg, 0.24 mmol) and Lindlar catalyst (10 mg) were suspended in 2 mL methanol in a 10 mL thick-walled tube. The tube was placed in a Parr hydrogenation/shaker apparatus, evacuated, and hydrogen gas introduced at 40 psi. The reaction was allowed to proceed for 16 hours at which time the reaction mixture was filtered through a short plug of Celite and rinsed with methanol. Removal of the solvent under vacuum provided a brown residue which was purified by flash column chromatography (5% ethyl acetate in hexanes) which gave the title compound as a yellow crystalline solid, 65 mg, 80%. R_f 0.4 (25% ethyl acetate in hexanes); mp 105/108 °C; IR (film) ν 2933, 1553, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.5 (s, 2H), 5.95 (s, 1H),

3.8 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.2, 129.9, 124.0, 119.8, 104.3, 60.4; HRMS-EI Calcd for $C_{12}H_{12}O_2S_2$ (M^+) 252.0279, Found: 252.0281.



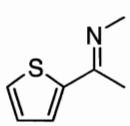
(Methyl-2-thienyl)-vinylacetate (494).

To a 100 mL round-bottomed flask under argon atmosphere was added freshly distilled (100 °C / 0.1 mm Hg) alcohol **492** (1.6 g, 12.5 mmol, 1 equiv), followed by DMAP (763 mg, 6.25 mmol, 0.50 equiv), and vinyl acetic acid (2.1 mL, 37.5 mmol, 3 equiv). The flask was cooled to 0 °C before addition of DCC (5.4 g, 16.25 mmol, 1.3 equiv), which initiated immediate precipitation of an off-white solid. The ice bath was removed after 1 h and the reaction mixture continued to stir for an additional 4 h. Filtration of the precipitate through Celite and concentration of the resulting solution under vacuum produced an orange residue, which was purified by flash column chromatography using cyclohexane as eluent. Purification of the residue gave a **494** as a clear and colorless oil, 875 mg, 36%: R_f 0.39; (hexanes-ethyl acetate, 5:1); IR (neat) ν 2983, 2933, 1738, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 5.0, 1H), 7.06 (d, J = 3.6 Hz, 1H), 7.00 (dd, J = 5.2, 1.5 Hz, 1H), 6.18 (q, J = 13.3, 7.0 Hz, 1H); 5.92 (m, 1H), 5.19 (m, 1H), 5.17 (m, 1H), 3.11 (dd, 4.1, 1.7 Hz, 1H), 3.08 (dd, 4.1, 1.7 Hz, 1H), 1.64, (d, J = 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 144.4, 130.0, 126.5, 125.3, 125.2, 118.6, 67.8, 39.2, 22.0; HRMS-EI Calcd for $C_{10}H_{12}O_2S$: 196.0558; Found 196.0562.



3-Methyl-but-ene-oic acid-(1-thiophene-2-yl)-ethyl ester (497)

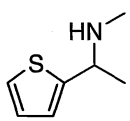
Alcohol **492** (641 mg, 5.0 mmol, 1 equiv) was dissolved in 40 mL anhydrous methylene chloride and cooled to 0 °C. To this solution was added 3-methyl-but-3-en-oic acid **496** (651 mg, 6.5 mmol, 1.3 equiv), DMAP (184 mg, 1.5 mmol, 0.3 equiv), and DCC (1.24 g, 6.0 mmol, 1.2 equiv), and the mixture stirred overnight, slowly warming to rt. The white precipitate was filtered and the filtrate concentrated under reduced pressure. The crude oil was purified by flash column chromatography (5% ethyl acetate in hexanes) to provide the ester as a clear and colorless oil, 350 mg, 33%. R_f: 0.38 (10% ethyl acetate in hexanes); IR (film) ν 2981, 2933, 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (m, 1H), 6.98 (m, 1H), 6.88 (m, 1H), 6.11 (q, J = 13.2 Hz, 1 H), 4.82 (s, 1H), 4.76 (s, 1H), 2.91 (s, 2H), 1.71 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ:170.5, 144.3, 138.4, 126.5, 125.2, 125.2, 114.7, 67.7, 43.6, 34.9, 22.4, 21.9; Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; Found: C, 62.91; H, 6.96.



Methyl-(1-thiophen-2-yl-ethylidene)-amine (500)[202]

A 150 mL thick-walled reaction tube equipped with magnetic stirring bar was charged with 2-acetylthiophene **491** (10g, 79.0 mmol, 1.0 equiv) in 35 mL toluene. The flask was cooled externally to -40 °C and gaseous methylamine was bubbled through the stirred solution for a period of 15 min. Activated molecular sieves (5 g, 4Å) were introduced

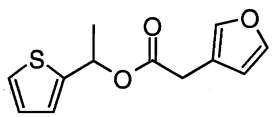
followed by *p*TsOH (150 mg, 7.9 mmol, 1 equiv). The flask was capped and placed in an oil bath heated externally to 60 °C. After 48 h, analysis of an NMR aliquot of the crude reaction mixture indicated a full conversion to the imine. The crude reaction mixture was filtered through a layer of Celite and the Celite washed with methylene chloride. Evaporation of the solvent under reduced pressure provided the title compound as a yellowish-orange oil which required no further purification (quantitative conversion). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41-7.25 (m, 2H), 7.10-6.90 (m, 1H), 3.28 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.8, 147.6, 128.4, 127.2, 126.4, 39.0, 15.0; IR (neat) 1624 cm^{-1}.



1-thienyl-1-methylaminoethane (501).

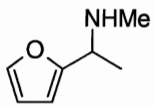
Imine **500** (6.5 g, 46.8 mmol, 1.0 equiv) was dissolved in 40 mL methanol and transferred to a 100 mL round-bottomed flask under argon atmosphere. The flask was cooled externally by means of an ice/water bath before addition of sodium borohydride (3.45 g, 97.3 mmol, 2.0 equiv) in one portion. The reaction mixture was allowed to stir for 12 h before being quenched by addition of 15 mL of a 15% aqueous solution of sodium hydroxide. Methanol was removed under reduced pressure and the residue extracted with chloroform (5 x 25 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$ and charcoal. Filtration and removal of the solvent provided the title compound as a light yellow oil, which required no further purification, (4.45 g, 68% yield); IR (neat) ν 3305 (broad), 2972, 1475 cm^{-1}; ^{1}H NMR (300 MHz,

$CDCl_3$) δ: 7.22 (d, J = 4.8 Hz, 1H), 6.99-6.93 (m, 2H), 3.98 (q, J = 6.6 Hz, 1H), 2.40 (s, 3H), 1.41 (d, J = 8.7 Hz, 3H).



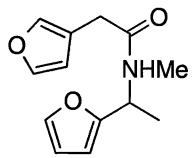
Furan-3-yl-acetic acid (1-thiophen-2-yl-)ethyl ester (499)

A 5 mL flame-dried flask under argon atmosphere was charged with (thienyl)-1-ethanol **492** (202 mg, 1.58 mmol, 1.0 equiv) dissolved in 1.5 mL anhydrous methylene chloride. The flask was cooled externally to 0 °C by means of an ice/water bath. EDC (333 mg, 1.73 mmol, 1.1 equiv), carboxylic acid **498** (200 mg, 1.58 mmol, 1.0 equiv), and DMAP (20 mg, 0.158 mmol, 0.1 equiv) were added sequentially. The reaction mixture was allowed to slowly warm to rt over 2.5 h before being diluted with 10 mL methylene chloride and quenched with 2 mL of 1 N solution of HCl. The aqueous portion was extracted with methylene chloride, and the organic layers combined and washed with brine. After drying over $MgSO_4$, the organic extracts were filtered through a short column of silica gel to remove residual impurities. Evaporation of the solvent provided **499** as a clear and colorless oil which required no further purification, (187 mg, 62%). R_f 0.4 (hexanes-ethyl acetate, 4:1); IR (film) ν 2982, 2930, 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.29 (d, J = 3 Hz, 2H), 7.15 (m, 1H), 6.98 (m, 1H), 6.89 (m, 1H), 6.29 (s, 1H); 6.13 (dq, J = 6.6, 1.2 Hz, 1H), 3.39 (s, 2H), 1.59 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 144.2, 142.9, 140.4, 126.6, 125.4, 125.3, 117.1, 111.3, 68.1, 31.1, 22.0; HRMS-EI calcd for $C_{12}H_{12}O_3S$ (M^+), 236.1006; found, 236.0507.



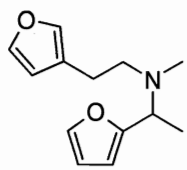
1-[2-Furanyl]-1′-aminomethyl-ethane (510)

Furan-2-methyl imine (1.0 g, 8.13 mmol, 1.0 equiv) was dissolved in 4 mL methanol and transferred to a 10 mL flask equipped with reflux condenser. The flask was cooled externally to 0 °C before addition of sodium borohydride (368 mg, 9.75 mmol, 1.2 equiv). The ice bath was removed and replaced with a warm water bath for 30 min. After cooling to rt and stirring for 4 h, the reaction was quenched by addition of 3 mL of 15% aqueous solution of NaOH. The volume of the reaction was reduced to approximately half under reduced pressure, and the remaining solution diluted with a saturated sodium chloride solution and extracted with chloroform. The aqueous layer was repeated extracted with chloroform and the combined extracts washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent removed under reduced pressure to provide 833 mg of a yellowish oil. The oil was purified by Kugelrohr distillation (200 °C / 80 mm Hg), affording the title compound as a clear and colorless oil, 570 mg (56% yield). IR (neat) ν 3290 (broad), 2978, 1649, 1374 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.37 (m, 1H), 6.34 (dd, J = 3.0, 1.8 Hz, 1H), 6.15 (d, J = 3.3 Hz, 1H), 3.78 (q, J = 6.9 Hz, 1H), 2.36 (s, 3H), 1.44 (bs, 1H), 1.42 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.6, 141.3, 109.8, 105.3, 52.8, 33.7, 19.8.



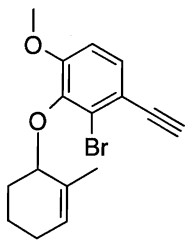
(*N*-Methyl-*N*-[2-furanyl]-1-ethane)-3-furanyl-3-acetamide (511)

A 25 mL round-bottomed flask under argon atmosphere was charged with amine (500 mg, 4.0 mmol, 1.0 equiv) in 4 mL distilled methylene chloride. The flask was cooled to 0 °C before sequential addition of DMAP (46 mg, 0.4 mmol, 0.1 equiv), EDC (843 mg, 4.40 mmol, 1.1 equiv), and carboxylic acid **498** (572 mg, 4.0 mmol, 1.0 equiv). The reaction mixture was slowly allowed to warm to rt over a 3.5 h period before being diluted with 20 mL of methylene chloride. The organic solution was washed with 2 mL of a 1N solution of HCl, 15% NaOH, and brine, and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent was removed in vacuo to provide 1.65 g of an orange oil. The oil was purified by flash column chromatography (4:1 hexanes, ethyl acetate) to afford the amide as a light yellow oil and mixture of major and minor rotamers, 810 mg (87%). R_f 0.56 (hexanes/ ethyl acetate, 1:1); IR (neat) 3117, 2981, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.41 (m, 1H), 7.38 (s, 2H), 6.41 (m, 1H), 6.33 (m, 1H), 6.20 (m ,1H), 6.00-**major rotamer** (q, J = 9.3 Hz, 1H), 5.14-**minor rotamer** (q J = 6.6 Hz, 1H), 3.72- **minor rotamer** (q, J = 15.9 Hz, 2H), 3.55 (s, 2H), 2.71 (s, 3H), 1.47-**minor rotamer** (d, J = 8.1 Hz, 3H), 1.44-**major rotamer** (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.3, 170.2, 154.3, 153.4, 143.09, 143.00, 142.4, 142.2, 140.0, 118.6, 118.3, 111.3, 110.1, 110.0, 107.5, 107.3, 50.4, 45.0, 31.1, 30.8, 29.8, 27.4, 16.3, 15.1; HRMS-EI calcd for $C_{13}H_{15}NO_3$ (M^+): 233.1051, found: 233.1057; Anal. calcd for $C_{13}H_{15}NO_3$ C, 66.94; H, 6.48; Found C, 66.68; H, 6.44.



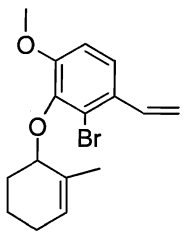
(*N*-Methyl-*N*-[2-furanyl]-1-ethane)-1-[3-furanyl]-2-ethylamine (512).

A 10-mL round-bottomed flask equipped with reflux condenser under argon atmosphere was charged with furan derivative **511** (300 mg, 1.28 mmol, 1 equiv). The furan was dissolved in a mixture of 3 mL ethyl ether and 5 mL THF and the flask cooled externally by means of an ice bath. LAH (97 mg, 2.57 mmol, 2.0 mol equiv) was added in a single portion to the solution of furan. The mixture was heated to refluxing temperature for a period of 14 h. The flask was again cooled and the reaction quenched by *careful* addition of 100 μL distilled water, 200 μL of 15% (aq) NaOH solution, and 300 μL distilled water. The so-formed aluminate salts were filtered and washed with warm ether. The filtrate was diluted with 10 mL of fresh ether and 1 mL brine. The layers were separated and the aqueous portion extracted with three portions of ether. The combined ethereal layers were washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the ether removed by evaporation to provide 261 mg of an oil which required no further purification, 52%. R_f 0.35 (hexanes-ethyl acetate, 1:1); IR (neat) ν 2977, 2939, 2849, 1502 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.36 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 5.4 Hz, 1H), 6.33 (m, 1H), 6.28 (s, 1H), 6.14 (m, 1H), 3.94 (q, J = 6.9 Hz, 1H), 2.61 (m, 4H), 2.27 (s, 3H), 1.39 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ:156.1, 142.5, 141.4, 139.1, 123.1, 111.1, 109.6, 106.7, 56.1, 54.3, 37.7, 23.7, 14.8; HRMS-EI Calcd for $C_{13}H_{17}NO_2$ (M^+): 219.1259, Found: 219.1262.



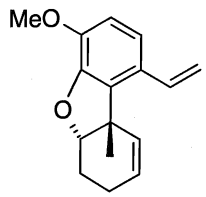
2-Bromo-1-ethynyl-4-methoxy-3-(2-methyl-cyclohex-2-enyloxy)-benzene (523).

A solution of alcohol **522** (98 mg, 0.88 mmol, 1 equiv) in 15 mL distilled THF was transferred to 50 mL round-bottomed flask under argon atmosphere, and the flask cooled to an external temperature of -30 °C. To this was added tri-*n*-butyl phosphine (438 μL, 1.76 mmol, 2.0 equiv) was added by syringe in a single portion. DIAD (342 μL, 1.76 mmol, 2.0 equiv) was added dropwise over 10 min to the solution. Simultaneously, a solution of phenol **518** (200 mg, 0.88 mmol, 1.0 equiv) in 2 mL of distilled THF was added by syringe over 10 min. The reaction mixture was allowed to slowly warm to rt over a 24 h period. The crude reaction mixture was filtered through a short column of silica and the filtrate concentrated under reduced pressure. The residue was chromatographed on silica (9:1 pentane, ethyl acetate) to furnish the aromatic ether **523** as clear oil which solidified on trituration with diethyl ether, (170 mg, 60% yield). Mp 88/91 °C (from MeOH); R_f 0.29 (hexanes-ethyl acetate, 9:1); IR (neat) ν 3290, 2939, 2837, 2107, 1585, 1478 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.28 (d, J = 8.7 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 5.74 (s, 1H), 4.74 (m, 1H), 3.87 (s, 3H), 3.29 (s, 1H), 2.10-2.00 (m, 3H), 1.90 (s, 3H), 1.58-1.48 (m, 3H); ^{13}C NMR (600 MHz, $CDCl_3$) δ: 154.4, 145.2, 133.1, 129.0, 127.7, 122.0, 117.4, 111.0, 82.3, 79.8, 78.6, 55.7, 28.3, 25.5, 21.2, 18.2; HRMS-EI Calcd for $C_{16}H_{17}BrO_2$ (M^+): 322.0392, Found: 322.0392; Anal. calcd for: $C_{16}H_{17}BrO_2$: C, 59.83; H, 5.33; found: C, 59.99; H, 5.50.



2-Bromo-4-methoxy-3-(2-methyl-cyclohex-2-enyloxy)-1-vinylbenzene (525)

A solution of DIAD (365 μL, 1.86 mmol, 1.1 equiv) in 5 mL THF at 0 °C was treated dropwise with tri-*n*-butylphosphine (0.46 mL, 1.86 mmol, 1.1 equiv). Disappearance of the characteristic yellow color accompanied the addition of phosphine. After stirring 10 min, the solution of phosphine/DIAD was transferred by syringe over 5 min to a 100 mL flask containing 2-bromo-6-methoxyl-3-vinyl phenol (371 mg, 1.62 mmol, 1.0 equiv) and allylic alcohol **522** (176 mg, 1.45 mmol, 0.9 equiv) in 50 mL THF at 0 °C. A bright yellow color appeared on addition of the phosphine/DIAD complex. The reaction mixture was stirred at 0 °C for a period of 4 h and then concentrated under reduced pressure to give a yellow residue. Purification of the oil by flash column chromatography (9:1, hexanes, ethyl acetate) gave 399 mg (76%) of the aryl ether as a clear and colorless oil. R_f 0.58 (Pentane/ Et_2O, 9:1); IR (film) 2938, 2837, 1623, 1586, 1464, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.29 (m, 2H), 7.06 (dd, J = 17.1, 6.3 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 5.72 (m, 1H), 5.61 (dd, J = 17.4, 0.9 Hz, 1H), 5.25 (dd, J = 10.8, 0.9 Hz, 1H), 4.75 (m, 1H), 3.87 (s, 3H), 2.20-2.00 (m, 3H), 1.96 (s, 3H), 1.70-1.45 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.1, 144.6, 136.0, 133.3, 131.5, 127.4, 121.1, 120.2, 114.6, 111.2, 78.4, 55.8, 28.3, 25.5, 21.2, 18.3 ; MS-EI: 244 (9.2), 230 (96.2), 228 (100), 215(15.9), 213 (15.1), 133 (16.8), 95 (72.1), 79 (42.3)

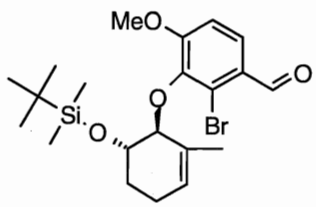


6-Methoxy-9b-methyl-9-vinyl-3,4,4a,9b-tetrahydrodibenzofuran (526).

A 10-mL Teflon capped thick-walled sealed tube containing a magnetic stirring bar was charged with aryl ether **525** (52 mg, 0.155 mmol, 1.0 equiv) dissolved in 7 mL distilled and degassed benzene under a positive pressure of nitrogen. To the resulting solution was added a catalytic amount (18 mg, 0.016 mmol, 0.1 equiv) of $Pd(PPh_3)_4$, triphenyl phosphine (10 mg, 0.037 mmol, 0.23 equiv), and Proton Sponge™ (66 mg, 0.310 mmol, 2.0 equiv). The yellow solution was heated externally to an external temperature of 90 °C for a period of 15 h. Progress of the reaction was monitored by TLC and after 15 h an additional 20 mg of catalyst was added and the reaction mixture heated for an additional 4 h period. The reaction mixture was cooled to rt and diluted with 50 mL of diethyl ether. The ethereal solution was washed with a saturated solution of aq NH_4Cl (5 x 1 mL) and brine (2 x 1 mL). The organic phase was dried over anhydrous MgSO4. Filtration of the drying agent and evaporation of the solvent gave a crude brown oil, which was purified by flash column chromatography to provide the title compound as a slightly yellowish oil, (4 mg, 11% yield) and returned 10 mg starting material (20%).

R_f 0.33 (pentane: ether, 9:1); ^1H NMR (300 MHz, $CDCl_3$) δ: 6.99 (d, J = 8.4, 1H), 7.00 (m, 1H), 6.94 (d, J = 8.4, 1H), 5.78 (s, 2H), 5.59 (dd, J = 17.4, 1.2 Hz, 1H), 5.27 (dd, J = 11.1, 1.2, 1H), 4.59 (s, 1H), 3.89 (s, 3H), 2.31-2.28 (m, 2H), 1.98-1.96 (m, 2H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.0, 144.4, 133.0, 130.4, 128.0, 126.3, 118.4,

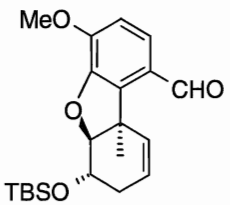
114.1, 111.2, 87.7, 77.2, 55.9, 45.8, 26.1, 22.9, 19.2; HRMS-EI calcd for $C_{16}H_{18}O_2$ (M^+):242.1301, found: 242.1304.



2-Bromo-3-[1(*S*),(6(*S*)-(*tert*-butyl-dimethyl-siloxy)-2-methyl-cyclohex-2-enyloxyl]-4-methoxy-benzaldehyde (528).

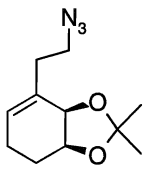
Aryl bromide **302** (343 mg, 1.49 mmol, 1.0 equiv) and alcohol **527** (360 mg, 1.49 mmol, 1.0 equiv) were dissolved in 40 mL distilled THF and the solution cooled to an external temperature of 0 °C. In a separate flask, nBu$_3$P (406 μL, 1.63 mmol, 1.1 equiv) was added over one min to a solution of DIAD (331 mg, 1.63 mmol, 1.1 equiv) in 5 mL THF under a argon atmosphere at 0 °C. Disappearance of the deep yellow color accompanied the addition of the phosphine. After 10 min, the colorless solution of the phosphine/DIAD complex was transferred over 5 min to the pre-cooled solution of the alcohol and phenol and a deep yellow color change was observed. The reaction mixture was slowly warmed to rt overnight. Evaporation of the solvent gave a brown oil, which was purified by column chromatography to afford 170 mg of the pure aldehyde (25%) as well as 130 mg of material of lower purity (19%). $[\alpha]^{20}_D$: +92.6 (c 0.5, $CHCl_3$); R_f 0.13 (hexanes: ethyl acetate, 95:5); IR (film) 2952, 2929, 1687, 1578, 1562, 1481 cm^{-1}; ^{1}H NMR (300 MHz,$CDCl_3$) δ: 10.28 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 5.79 (s, 1H), 4.46 (s,1H), 4.02 (s, 1H), 3.95 (s, 3H), 2.12-2.17 (m, 2H), 2.03-2.02 (m, 1H), 1.88 (s, 3H), 1.70-1.68 (m, 1H), 0.75 (s, 9 H), -0.12 (s, 3H), -0.17 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.2, 158.1, 144.9, 129.5, 128.3, 127.5, 125.8, 123.3, 110.8, 81.6, 67.8, 55.9, 25.6, 25.3, 21.7, 20.7, 18.0, -4.9, -5.1; HRMS-EI (M^+) Calcd: 454.1175; Found: 454.1181.



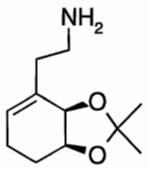
(5*S*,6*S*,9*R*)-6-(*tert*-Butyl-dimethyl-siloxy)-4-methoxy-9a-methyl-5a,6,7,9a-tetrahydro-dibenzofuran-1-carboxaldehyde (529).

Aromatic ether **528** (262 mg, 0.57 mmol, 1 equiv) was dissolved in 8 mL of distilled and degassed toluene and the solution transferred to a Teflon-sealed Schlenk flask containing a magnetic stirring bar. Palladium acetate (19 mg, 0.086 mmol, 0.15 equiv), silver carbonate (474 mg, 1.73 mmol, 3 equiv), and *bis*-diphenylphosphinoferrocene (48 mg, 0.086 mmol, 0.15 equiv) were added sequentially. The flask was sealed and placed in a 80 °C oil bath for a period of 14 h. The flask was then cooled to rt and the black suspension filtered through a short column of Celite. The black solution was concentrated under reduced pressure and the residue purified by flash column chromatography to provide the title compound as a white solid, 175 mg, 81% yield. Mp 89-95 °C; $[\alpha]_D^{20}$ +102.4, (*c* 0.8, $CHCl_3$); R_f 0.33 (hexanes-ethyl acetate, 9:1); IR (film) ν 2929, 2855, 1693, 1610, 1571, 1435 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.98 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.32 (d, *J* = 9.9 Hz, 1H), 5.60 (m, 1H), 4.48 (d, *J* = 6.3 Hz, 1H), 4.12 (m, 1H), 3.94 (s, 3H), 2.36-2.14 (m, 2H), 1.63 (s, 3H), 0.92 (s, 9H), 0.139 (s, 3H), 0.068 (s, 3H) ppm ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.2, 149.9, 147.2, 130.4, 128.9, 126.4, 122.4, 110.3, 92.4, 67.5, 55.9, 48.4, 29.7, 27.0, 25.8, 25.6, 18.1, -4.8, -5.1; HRMS-EI calcd for $C_{17}H_{21}O_4Si$ (M^+-57): 317.1209, found:317.1203;



[3a*R*,7a*S*]-4-(2-azidoethyl)-2,2-dimethyl-3a,6,7,7a-tetrahydro-benzo[1,3]dioxole (539):

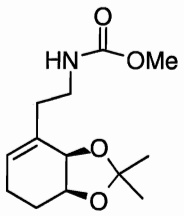
(1*S*,2*R*)-3-(2-azidoethyl)-cyclohex-3-ene-1,2-diol (10.0g, 54.6 mmol) was dissolved in 2,2-DMP (33 mL, 273 mmol, 273 mmol). A catalytic amount of *p*TsOH was added, and the reaction mixture stirred at rt for 18 h until complete conversion of starting material was observed by TLC, at which time the reaction was quenched by addition of 10 mL of a saturated solution of sodium carbonate, and excess 2,2-DMP was removed under reduced pressure. The resulting residue was diluted with 10 mL of distilled water and 75 mL of ethyl acetate. The layers were transferred to a separatory funnel and the aqueous layer drained. The aqueous layer was extracted with 3 portion of 50 mL ethyl acetate, and the combined organic portions washed with brine and dried over $MgSO_4$. Removal of the drying agent by filtration and evaporation of the solvent gave the title compound, which required no further purification for the subsequent transformation, (12.5 g, quantitative). An analytical sample of the azide was obtained by Kugelrohr distillation (175 °C/ 0.03 mm Hg), which provided a clear and colorless oil. R_f: 0.6 (hexanes, ethyl acetate; 4:1); $[\alpha]_D^{23}$ +44.3 (c 1.0, $CHCl_3$); IR (neat) 2985, 2932, 2094, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 1H), 4.38-4.32 (m, 2H), 3.44 (t, J = 7.2 Hz, 2H), 2.47-2.38 (m, 2H), 2.25-2.18 (m, 1H), 1.91 (m, 2H), 1.74 (m, 1H), 1.39 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 132.4, 127.8, 108.5, 73.6, 73.4, 49.6, 33.6, 27.9, 26.4, 25.3, 20.7 ppm; HRMS-FAB (NBA matrix) Calcd for $C_{11}H_{18}N_3O_2$ (M^+ +1): 224.1399, Found 224.1333.



[3a*R*,7a*S*]-4-(2-aminoethyl)-2,2-dimethyl-3a,6,7,7a-tetrahydro-benzo[1,3]dioxole (540).

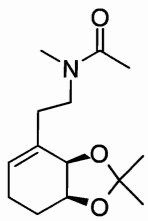
Azide **539** (10.0 g, 44.8 mmol, 1.0 equiv) was dissolved in 600 mL THF containing 2.4 mL distilled water and transferred to a 1-L round-bottomed flask equipped with reflux condenser. Triphenylphosphine (21.5 g, 80.6 mmol, 1.8 equiv) was added and the solution was heated to an external temperature of 55 °C for a period of 24 h, at which time the solution was cooled to rt and the solvent removed under reduced pressure. The residue was dissolved in 100 mL of methylene chloride and acidified with 40 mL of 1 N (aq) HCl. The layers were separated and the aqueous portion basified with 10% (w/v) NaOH until pH of approximately 10 was attained. The basified aqueous portion was extracted with methylene chloride (4 x 50 mL) and the organic layer was dried over Na_2SO_4 and charcoal. The resulting suspension was filtered through basic alumina to give the title compound as a slightly pinkish oil, (6.9 g, 78% yield).

$[\alpha]_D^{23}$ +23.7 (c 0.75, $CHCl_3$); IR (neat) 3362 (broad), 2983, 2927, 1576 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.68 (m, 1H), 4.37 (m, 1H), 4.31 (m, 1H), 2.92-2.78 (m, 2H), 2.2 (m, 1H), 2.17 (m, 2H), 1.97-1.86 (m, 2H), 1.73 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.26 (bs, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 133.7, 126.9, 108.2, 73.6, 73.5, 40.1, 38.5, 27.9, 26.4, 25.6, 20.8 ppm; HRMS-FAB (NBA matrix) Calcd for (M^+ + 1) $C_{11}H_{20}NO_2$: 198.1494, Found: 198.1472.



[3a*R*,7a*S*]-4-[*N*-methylcarbamoyl)ethyl]-2,2-dimethyl-3a,6,7,7a-tetrahydro-benzo[1,3]dioxole (541).

Amine **540** (2.0 g, 10.1 mmol, 1.0 equiv) was dissolved in 45 mL distilled methylene chloride and cooled to 0 °C before addition of distilled triethylamine (2.8 mL, 20.3, 2.0 equiv). After several minutes, methyl chloroformate was added in one portion. After 19 h, the solvent was removed under reduced pressure, and the residue subjected to purification by flash column chromatography (1:1 hexanes, ethyl acetate) to furnish **541** as a faint pink oil, (1.36 g, 52% yield). R_f 0.48 (hexanes-ethyl acetate, 2:1); $[\alpha]_D^{23}$ +15.2 (c 0.9, $CHCl_3$); IR (film) ν 3342, 2984, 2932, 1703, 1534 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.69 (m, 1H), 4.98 (bs, 1H), 4.34 (m, 2H), 3.67 (s, 3H), 3.35 (d, J = 6 Hz, 2H), 2.41 (m, 1H), 2.25-2.16 (m, 2H), 1.96-1.88 (m, 2H), 1.85-1.81 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.0, 133.1, 128.0, 108.3, 73.6, 73.4, 51.9, 39.3, 34.8, 27.9, 26.3, 25.6, 20.8; HRMS-EI (M^+-15) Calcd for $C_{12}H_{18}NO_4$: 240.1235; Found: 240.1240.

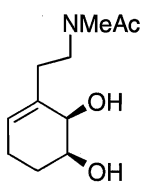


[3a*R*,7a*S*]-4-[2-(*N*-methylacetamido)ethyl]-2,2-dimethyl-3a,6,7,7a-tetrahydro-benzo[1,3]dioxole (542):

To a suspension of LAH (357 mg, 9.40 mmol, 2.0 mol equiv) in 30 mL THF at 0 °C was added a solution of methyl carbamate **541** in 10 mL ether over 10 min. Upon complete addition of the substrate, the cooling bath was removed, a reflux condenser was attached and the reaction mixture heated to reflux until complete consumption of the starting material (approximately 4 h). The reaction mixture was cooled to 0 °C and excess LAH was quenched by *careful* addition of 350 μL distilled water, 700 μL 15% (w/v) aq NaOH solution, and 1 mL distilled water. The white solid was separated from the organic solution by filtration, and the filtrate dried over anhydrous $MgSO_4$. Removal of the drying agent and evaporation of the solvent provided the expected amine **545** in quantitative yield. The material was used directly in the subsequent reaction.

The crude *N*-methyl derivative **545** (1.2 g, 5.67 mmol, 1.0 equiv) obtained from the procedure described above was dissolved in freshly distilled pyridine (1 mL) and methylene chloride (2 mL) and transferred to a 50 mL round-bottomed flask under argon atmosphere. The solution was cooled to 0 °C and freshly distilled acetic anhydride (580 μL, 6.26 mmol, 1.1 equiv) and DMAP (138 mg, 1.13 mmol, 0.2 equiv) were added to the solution. After 18 h, the reaction mixture was diluted with 70 mL methylene chloride and 10 mL of 1 N aq HCl. The layers were separated and the organic solution was washed with 10% (w/v) aq $CuSO_4$ (3 x 10 mL). The organic solution was dried over

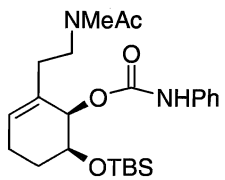
$MgSO_4$. Filtration of the drying agent and removal of the solvent under reduced pressure gave 1.32 g (92%) of the amide as a pale yellow oil. The material was of sufficient purity to be used directly in the subsequent step. An analytical sample was obtained by purification of the title compound by flash column chromatography, eluted with 10% MeOH in EtOAc. R_f 0.19 (100% EtOAc); $[\alpha]_D^{23}$ +5.83 (c 0.55, Et_2O); IR (film) ν 2984, 2933, 1627, 1558 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: Pair of rotamers, **A** and **B**. Rotamer **A**: 5.66 (m, 1H), 4.45 (m, 1H), 4.3 (m, 1H), 3.74 (m, 1H), 3.49-3.31 (m, 1H), 2.99 (s, 3H), 2.30-2.14 (m, 3H), 2.11 (s, 3H), 1.80-1.73 (m, 3H), 1.40 (s, 6H); Rotamer **B**: 5.66 (m, 1H), 4.32 (m, 2H), 3.49-3.31 (m, 2H), 2.94 (s, 3H), 2.30-2.14 (m, 3H), 2.06 (s, 3H), 1.80-1.73 (m, 3H), 1.40 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: (mixture of rotamers **A** and **B**) 170.5, 170.4, 133.4, 132.6, 127.9, 126.7, 108.5, 108.2, 74.07, 73.5, 73.4, 50.1, 49.5, 45.9, 36.0, 33.3, 33.2, 31.6, 27.9, 27.9, 26.4, 26.4, 25.5, 25.4, 21.9, 21.2, 20.9, 20.8 HRMS-EI Calcd for $C_{14}H_{23}NO_3$ (M^+): 253.1677, Found: 253.1684.



[1*S*,2*R*]-3-[2-(*N*-methyl)acetamidoethyl]-cyclohexa-3-ene-1,2-diol (543).

The protected diol **542** was dissolved in 2 mL of methanol and 2 mL of a solution of 3% conc HCl in MeOH was added. The mixture was stirred at rt for 48 h and then heated to reflux for 3 additional h. The solvent was removed under reduced pressure, and the residue purified by flash chromatography on silica gel ($CHCl_3$: MeOH, 9:1) to afford the diol as a clear and colorless oil, 140 mg (45%). R_f 0.25 ($CHCl_3$:MeOH, 9:1); $[\alpha]_D^{23}$ -128 (c 0.5, $CHCl_3$); IR (film) ν 3388, 2933, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ:

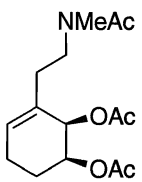
5.42 (t, J = 3.6 Hz, 1H), 4.30-4.21 (m, 1H), 4.01 (d, J = 3.9 Hz, 1H), 3.67-3.60 (dt, J = 10.8, 3.9 Hz, 1H), 3.03 (s, 3H), 2.93-2.89 (m, 1H), 2.37-2.28 (m, 2H), 2.06 (s, 3H), 1.73-1.59 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CHCl_3$) (mixture of rotational isomers) δ: 171.7, 170.5, 134.0, 128.4, 127.8, 69.9, 69.6, 69.4, 69.0, 50.3, 48.0, 36.1, 34.3, 33.4, 33.3, 25.5, 25.3, 24.4, 23.6, 21.7, 21.2 ; HRMS-EI Calcd for $C_{11}H_{19}NO_3$ (M^+): 213.1364, Found: 213. 1366.



(1*R*,6*S*)-Phenyl-carbamicacid-2-[2-(*N*-methyl)-acetamidoethyl]-(6-*tert*-butyldimethyl-silanoxy)-cyclohexa-2-enyl ester (544).

Alcohol **543** (100 mg, 0.30 mmol, 1.0 equiv) was dissolved in 2 mL of methylene chloride and 0.20 mL pyridine. The solution was cooled to 0 °C and phenyl isocyanate (132 μL, 1.2 mmol, 4.0 equiv) was added. DMAP (15 mg, 0.12 mmol, 0.4 equiv) was transferred to the reaction flask, and the resulting solution stirred for 48 h. After 18 h, the reaction mixture was diluted with 30 mL methylene chloride, washed with 10% (w/v) aq solution of $CuSO_4$ (2 mL x2), H_2O (2 mL x 2), and brine. The organic solution was dried over $MgSO_4$. Filtration of the drying agent and removal of the solvent gave a crude yellow oil, which was purified by column chromatography ($CHCl_3$/ MeOH, 97:3) to provide the title compound a white foam, (64 mg, 47%). R_f 0.28 (hexanes/ethyl acetate, 1:1); $[\alpha]_D^{24}$ -44.8 (c 3.1, $CHCl_3$); IR (film) ν 3255, 3134, 2928, 2856, 1724, 1632, 1603, 1546 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) mixture of rotational isomers **A** and **B** δ: Isomer **A**: 7.48 (m, 2H), 7.32-7.26 (m, 2H), 7.08-7.03 (m, 1H), 5.73 (m, 1H), 5.32 (d, J = 3 Hz, 1H); 4.06-4.02 (m, 1H), 3.92 (m, 1H), 3.39 (t, J = 7.8 Hz, 1H), 3.10 (m, 1H), 2.97 (s,

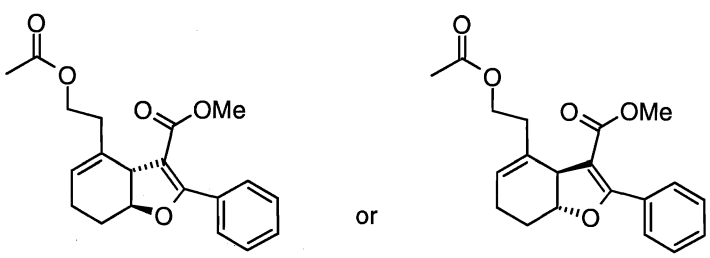
3H), 2.31-2.24 (m, 2H), 2.13 (s, 3H), 2.13-2.04 (m, 2H), 1.78-1.70 (m, 2H), 0.86 (s, 9H), 0.095 (s, 6H); Isomer **B**: 7.48 (m, 2H), 7.32-7.26 (m, 2H), 7.08-7.03 (m, 1H), 5.65 (s, 1H), 5.27 (s, 1H), 4.06-4.02 (m, 1H), 3.92 (m, 1H), 3.39 (t, J = 7.8 Hz, 1H), 3.10 (m, 1H), 2.90 (s, 3H), 2.31-2.24 (m, 2H), 2.13-2.04 (m, 2H), 2.09 (s, 3H), 1.70 (m, 2H), 0.86 (s, 9H), 0.077 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) mixture of indistinguishable rotational isomers **A** and **B** δ:170.7, 170.3, 153.9, 153.7, 138.5, 138.0, 132.0,131.8, 130.8, 130.2, 128.9, 128.8, 128.2, 123.3, 122.9, 118.6, 77.2, 72.4, 71.2, 69.3, 68.7, 68.1, 60.3, 50.4, 47.1, 50.4, 47.1, 36.1, 33.4, 33.0, 31.8, 26.8, 26.4, 25.7, 25.7, 24.2, 22.9, 21.9, 21.2, 18.1, -4.86, -4.99, -5.05.



(1R,6S)-Aceticacid-6-acetoxyl-2-[2-acetyl-methyl-amino)-ethyl]-cyclohex-2-enyl ester (14).

Protected diol **542** (1.22 g, 5.78 mmol, 1.0 equiv) was dissolved in 15 mL of methanol, and 5 drops of 37% aq HCl was added. After 19 h, the solvent was removed under reduced pressure, and the flask containing the resulting brown residue was then cooled to 0 °C. Pyridine (5 mL), which had previously been pre-cooled to 0 °C, was added followed by acetic anhydride (2.7 mL, 28.9 mmol, 5 equiv) in 2 mL methylene chloride. Finally, DMAP (140 mg, 1.15 mmol, 0.2 equiv) was added. After 4 h, the reaction mixture diluted with 50 mL chloroform, and the organic layer washed with 10% (w/v) aq $CuSO_4$ (10 mL x 4) and 1 N HCl (10 mL). The organic portion was dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave a brown oil, which was purified by passing through a column of silica gel and eluted with chloroform/ methanol

(95:5) to provide a clear and colorless oil, 755 mg (44% yield over two steps). R_f 0.26 ($CHCl_3$, MeOH, 9:1); $[\alpha]_D^{24}$ -102 (c 0.5, $CHCl_3$); IR (film) ν 3457, 2934, 1739, 1644, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: mixture of rotational isomers A and B: Isomer A: 5.76 (s, 1H), 5.54 (s, 1H), 5.01 (m, 1H), 3.54 (m, 1H), 3.34 (m, 1H), 2.98 (s, 3H), 2.26-2.17 (m, 4H), 2.13-2.10 (m, 9H), 1.91 (m, 1H), 1.61 (m, 1H); Isomer B: 5.76 (s, 1H), 5.54 (s, 1H), 5.01 (m, 1H); 3.36-3.29 (m, 2H), 2.92 (s, 3H), 2.26-2.17 (m, 4H), 2.13-2.10 (m, 9H), 1.91 (m, 1H), 1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: (mixture of rotational isomers) 170.7, 170.3, 170.2, 131.5, 130.6, 130.3, 129.0, 76.6, 73.4, 70.2, 69.8, 67.6, 67.6, 49.8, 46.6, 36.4, 33.2, 32.9, 31.5, 22.3, 22.2, 21.8, 21.1; HRMS-EI Calcd for $C_{15}H_{23}NO_5$ (M^+): 297.1576, Found: 297.1583.

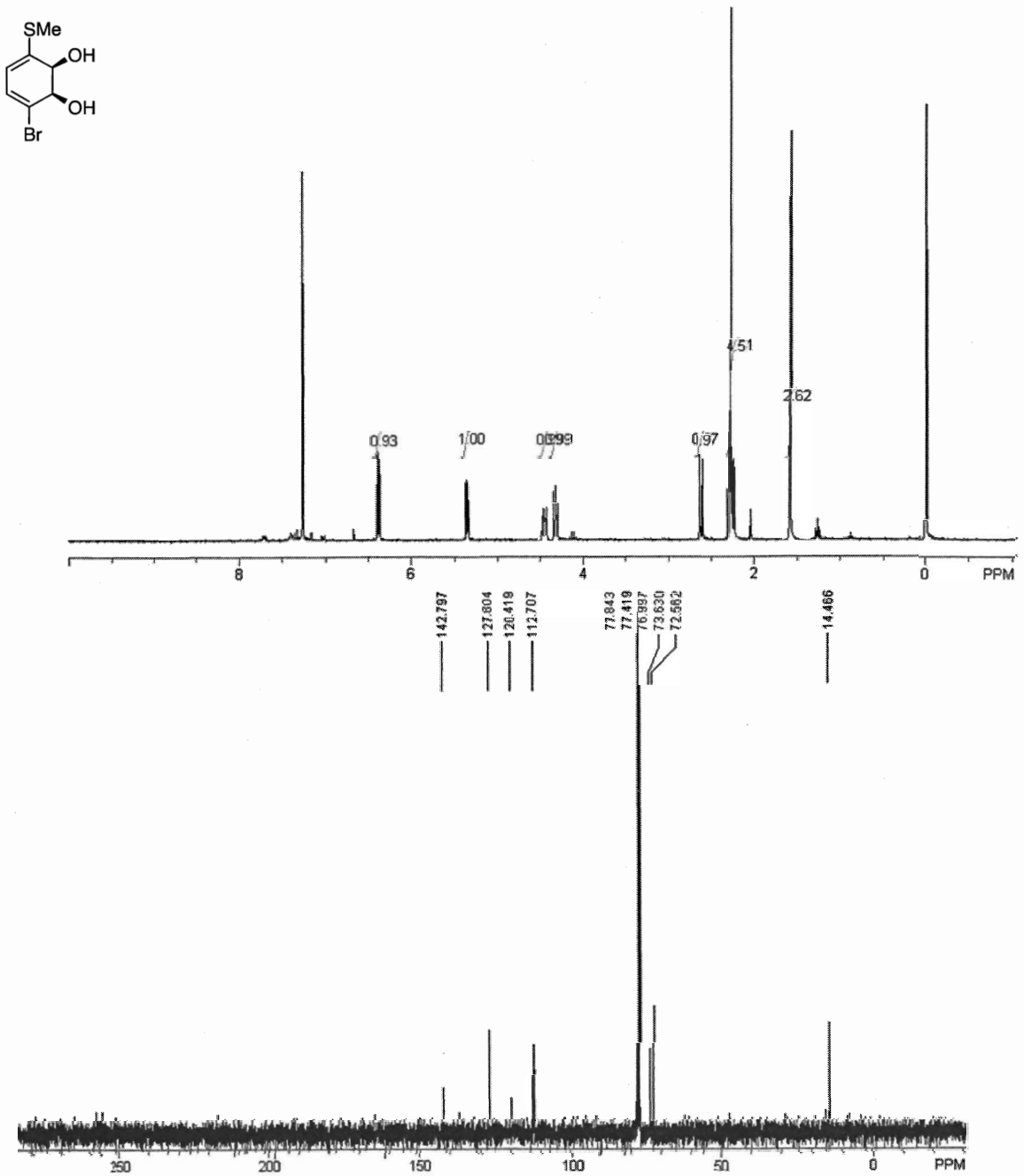


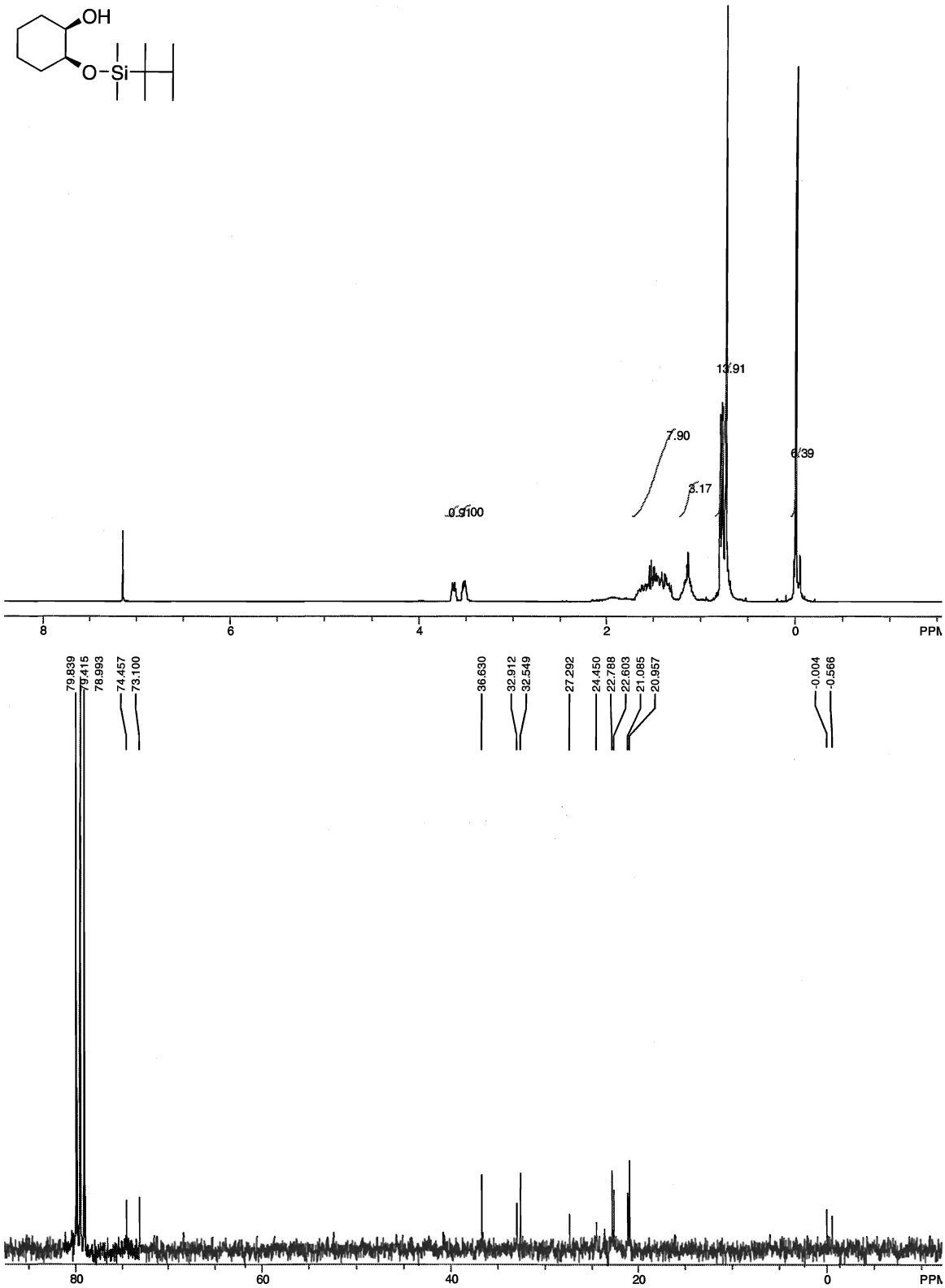
(3S,7S)-4-(2-Acetoxy-ethyl)-2-hydroxy-2-phenyl-2,3,3a,6,7,7a-hexahydro-benzofuran -3-carboxylic acid methyl ester (550a or 550b).

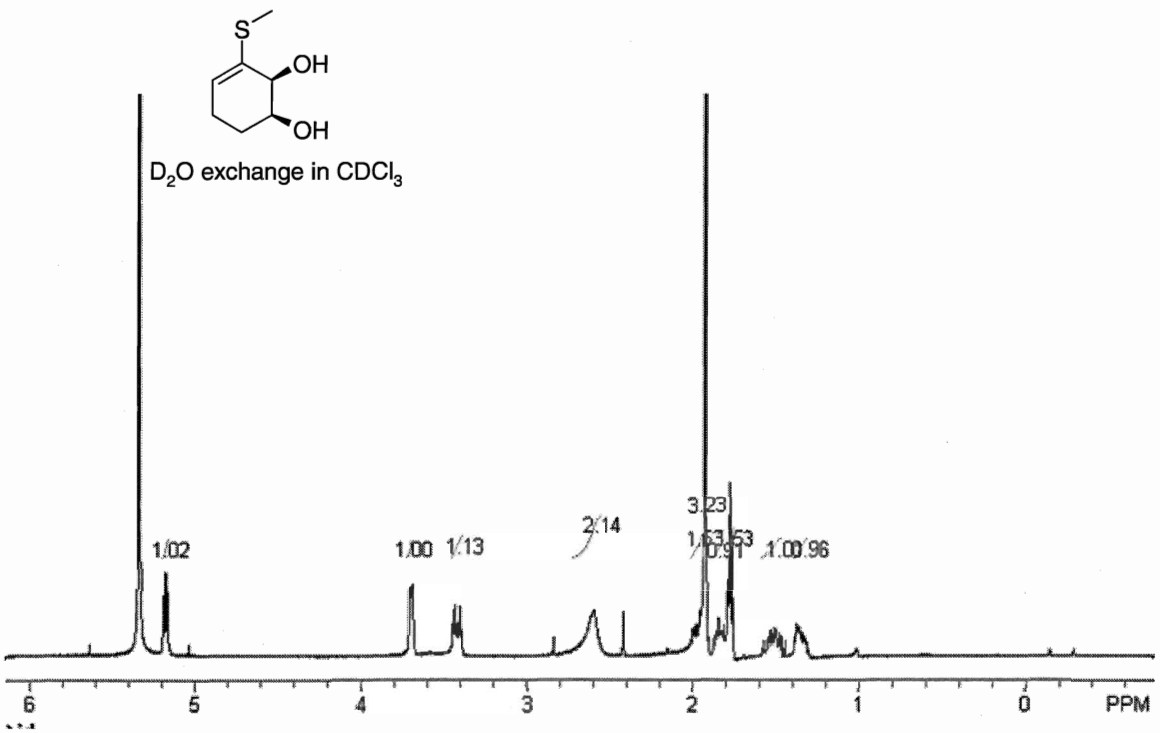
To a solution of triacetate **549** in 1 mL THF was added PPh_3 (20 mg, 0.3 equiv, 0.075 mmol) and $Pd(PPh_3)_4$ (18 mg, 0.015 mmol, 0.06 equiv), and the resulting mixture stirred at rt for 30 min. In a separate flask, β-ketoester **533** (156 mg, 0.88 mmol, 3.5 equiv) was added to a suspension of NaH (15 mg, 0.63 mmol, 2.5 equiv) in 2 mL of THF at rt. After 10 min, the resulting clear solution was transferred to the former mixture in a single portion. The combined reaction mixture was heated to reflux for 20 h, after which time the reaction mixture allowed to cool to rt, and the solvent was removed under reduced

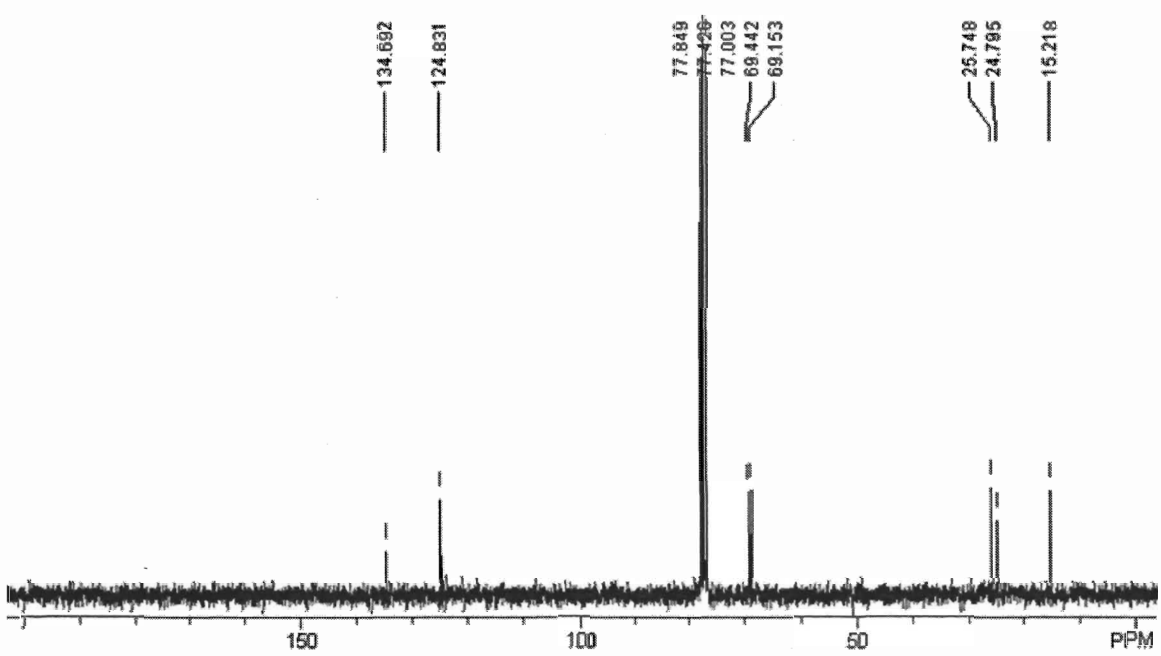
pressure. The residue was submitted to purification by column chromatography; elution with gave the title compound as a clear oil, 29 mg (27%). R_f 0.38 (hexanes-ethyl acetate, 9:1); $[\alpha]_D^{23}$ +161 (c 1.0, $CHCl_3$); IR (film) ν 3436 (broad), 3019, 1732, 1690, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75 (m, 2H), 7.41-7.34 (m, 3H), 5.95 (d, *J* = 5.4 Hz, 1H), 4.80 (d, *J* = 8.4, 1H), 4.36-4.28 (m, 1H), 4.24-4.16 (m, 1H), 3.67 (s, 3H), 3.22-3.14 (ddd, *J* = 13.3, 8.4, 4.5 Hz, 1H), 2.59-2.52 (m, 2H), 2.14-2.09 (m, 2H), 2.09 (s, 3H), 1.98-1.89 (m, 1H), 1.38-1.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.0, 165.8, 165.4, 130.7, 130.3, 130.2, 129.3, 127.6, 107.9, 80.0, 62.8, 50.8, 42.2, 33.5, 25.1, 23.1, 20.9; HRMS-EI (M^+) Calcd for $C_{12}H_{22}O_5$: 342.1452; Found: 342.1469; Anal. calcd for $C_{12}H_{22}O_5$: C, 70.16; H, 6.48; found: C, 69.70; H, 6.55.

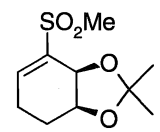
VI. Selected Spectra



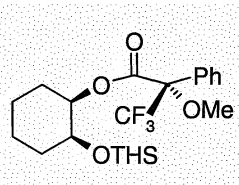

OH
O
Si
13.91
7.90
6.39
8.17
0.9100
8
6
4
2
0
PPM
79.839
79.415
78.993
74.457
73.100
36.630
32.912
32.549
27.292
24.450
22.788
22.603
21.085
20.957
-0.004
-0.566
80
60
40
20
0
PPM


S
OH
OH
D2O exchange in CDCl3
1.02
1.00
1.13
2.14
3.23
0.91
1.00
0.96
6
5
4
3
2
1
0
PPM

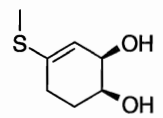

134.692
124.831
77.849
77.426
77.003
69.442
69.153
25.748
24.795
15.218
150
100
50
PPM


SO2Me
O
O

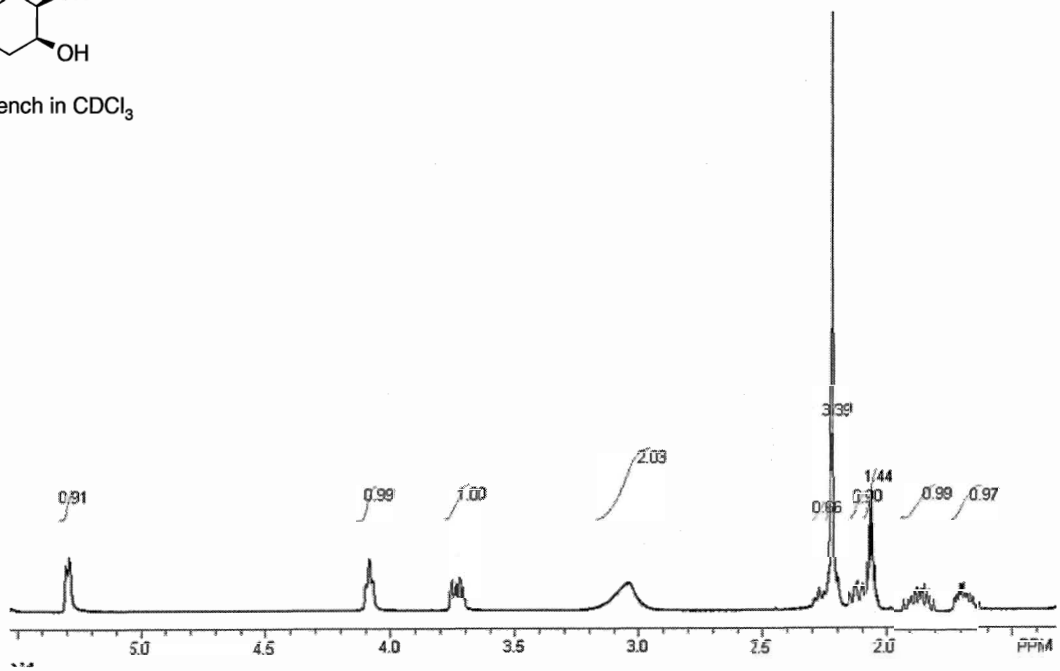
0.95
0.96
1.00
3.09
1.02
1.01
1.02
1.01
6.27
10
8
6
4
2
PPM

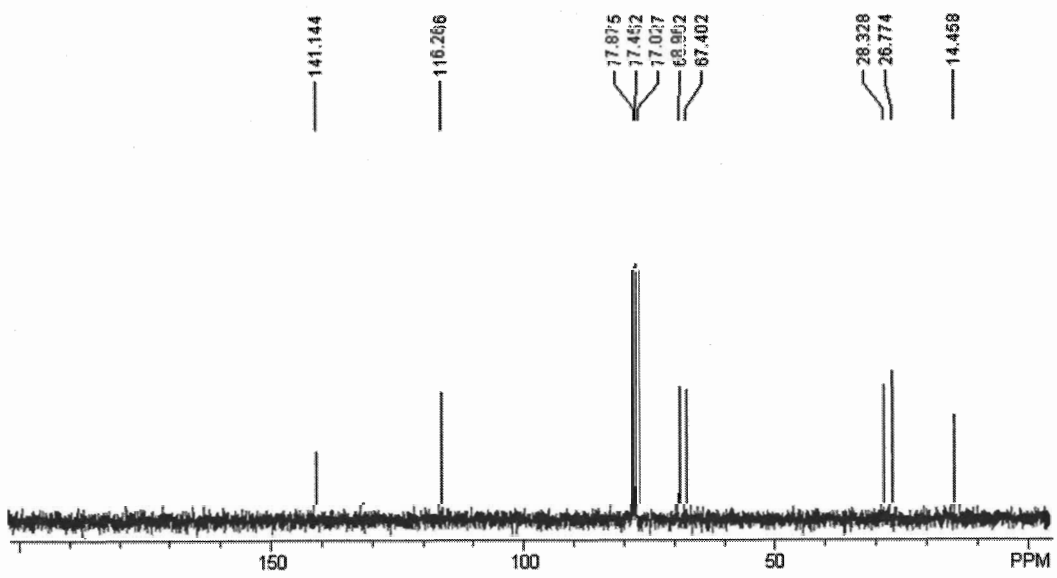

O
O
Ph
CF3
OMe
OTHS

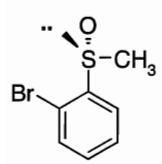
2.12
3.49
1.00
1.11
3.59
1.21
8.49
3.33
15.66
3.49
3.51
8
6
4
2
0
PPM



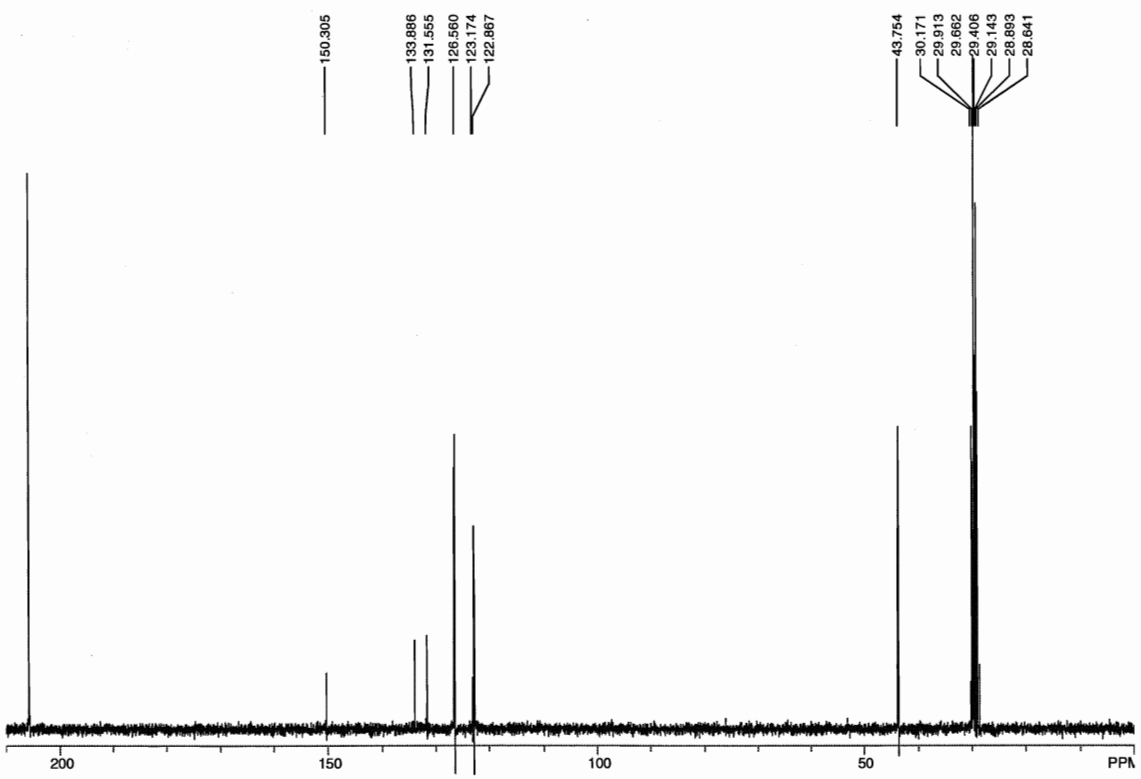
D_2O quench in $CDCl_3$

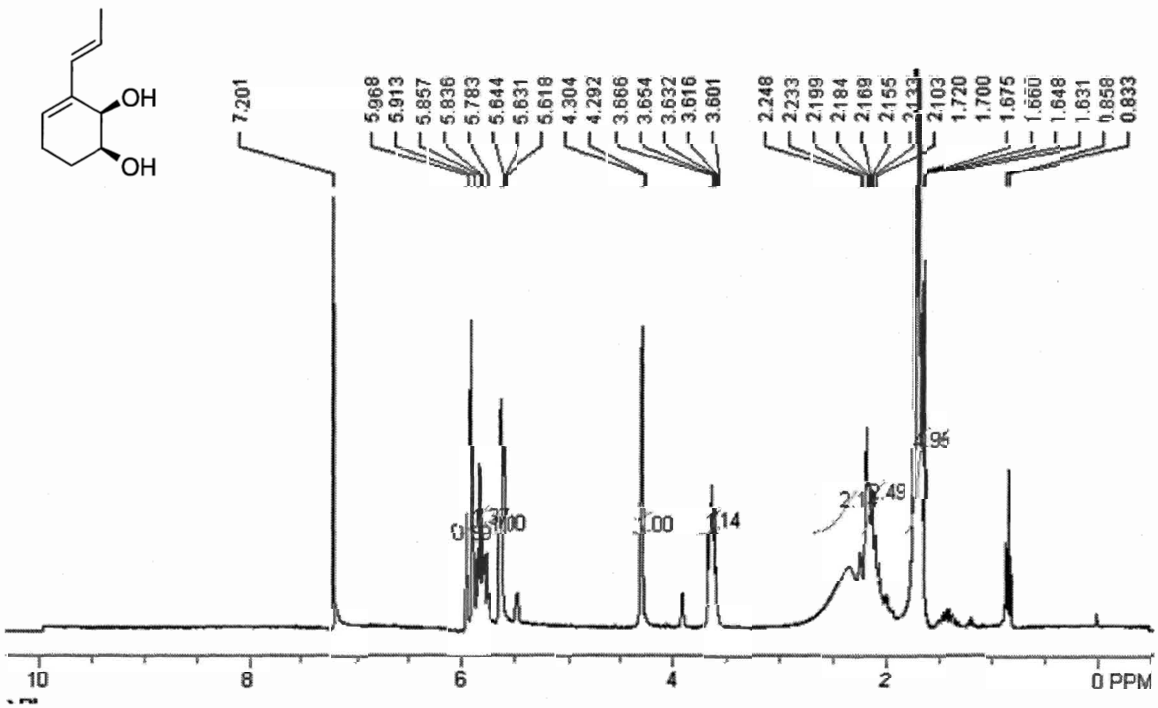


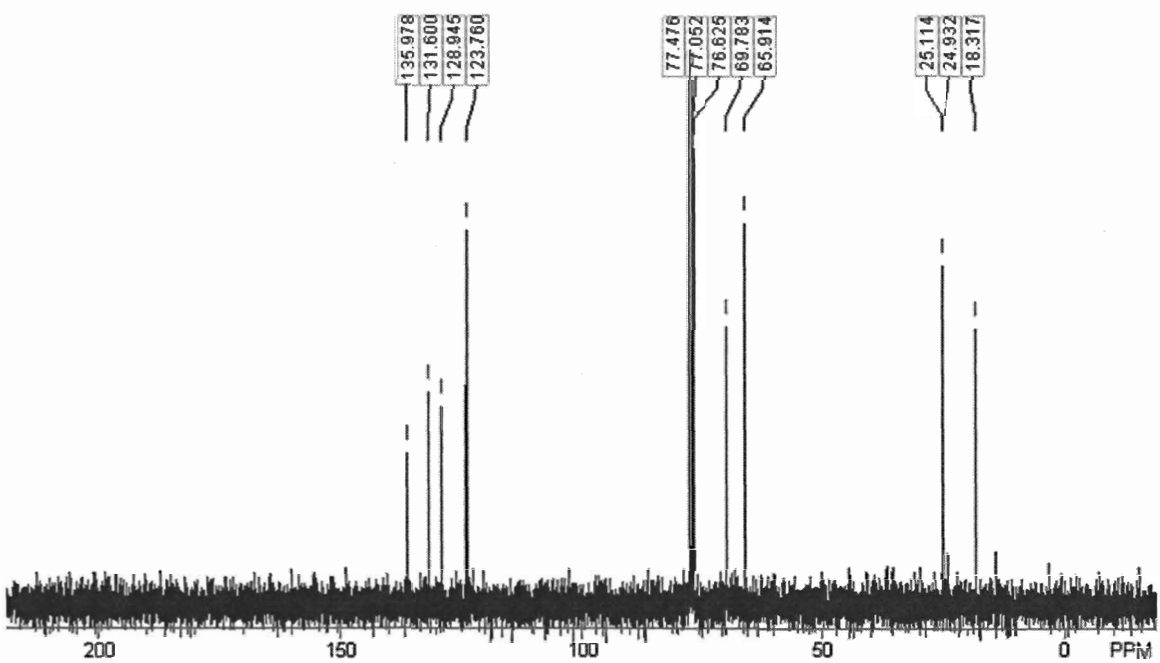


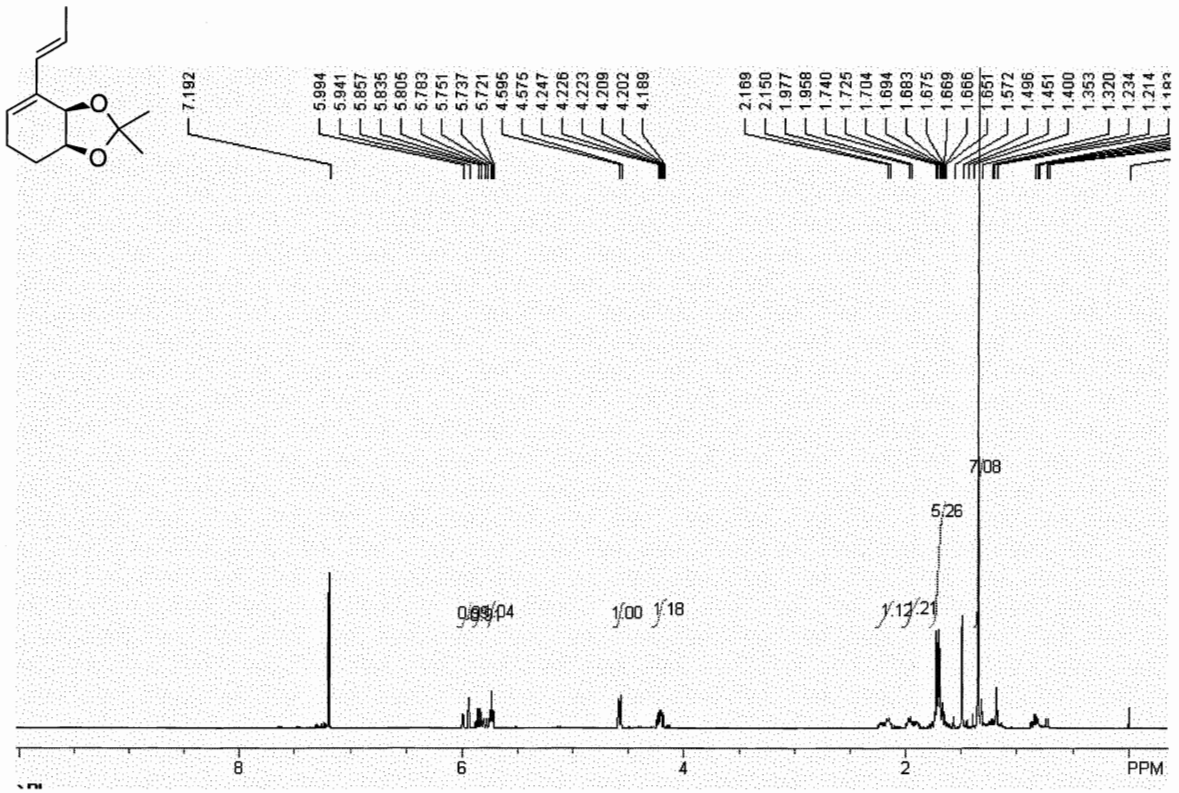

O
S–CH3
Br

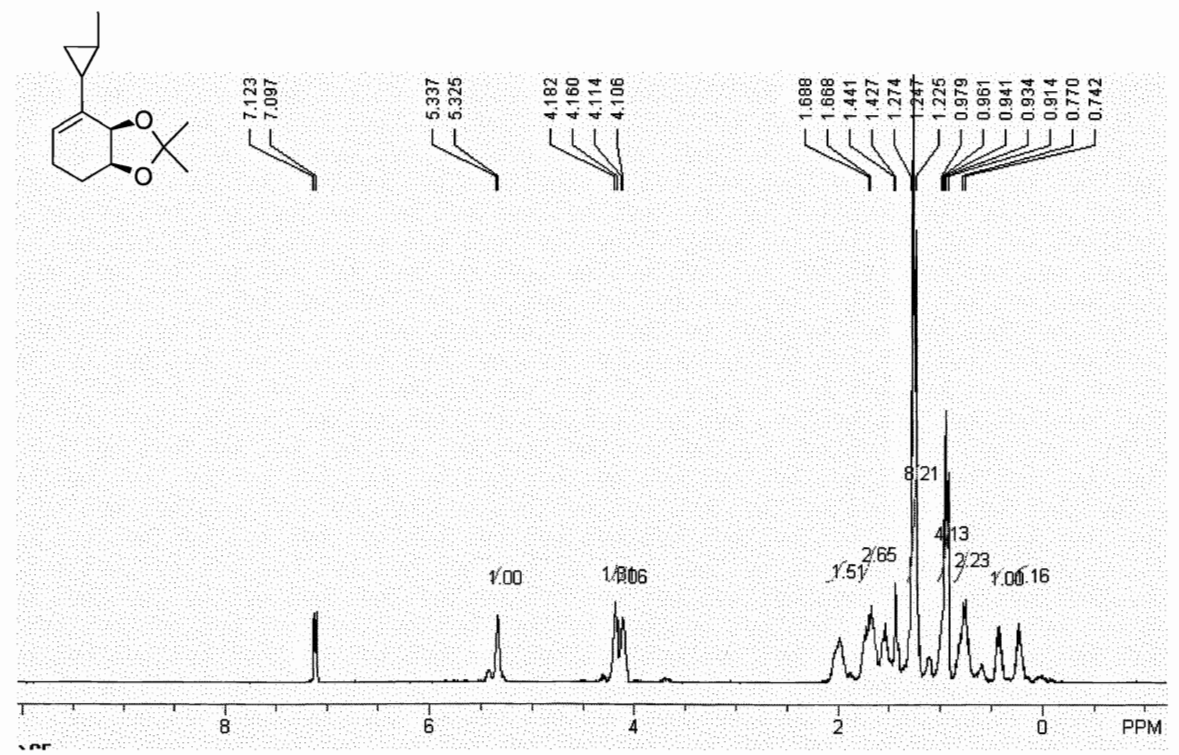
3.00
1.78
0.84
0.96
10
9
8
7
6
5
4
3
2
PPM

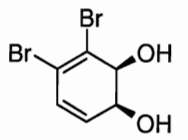

150.305
133.886
131.555
126.560
123.174
122.867
43.754
30.171
29.913
29.662
29.406
29.143
28.893
28.641
200
150
100
50
PPM


OH
OH
7.201
5.968
5.913
5.857
5.836
5.783
5.644
5.631
5.618
4.304
4.292
3.666
3.654
3.632
3.616
3.601
2.248
2.233
2.199
2.184
2.169
2.155
2.133
2.103
1.720
1.700
1.675
1.660
1.648
1.631
0.858
0.833
1.00
1.14
2.49
10
8
6
4
2
0 PPM

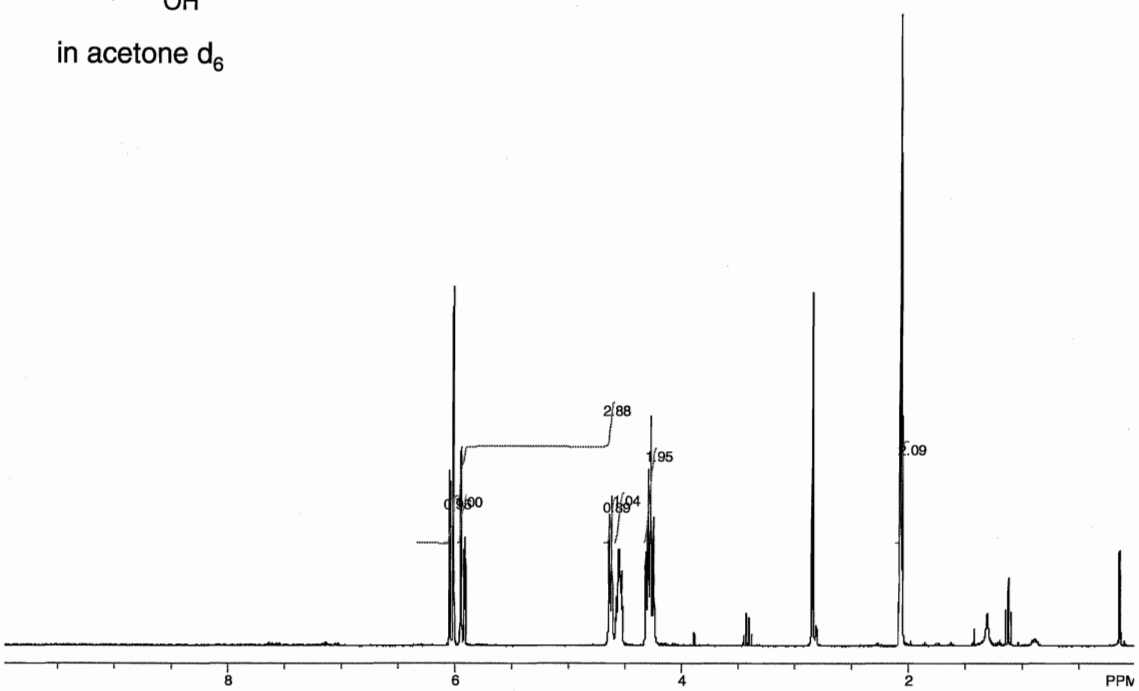

135.978
131.600
128.945
123.760
77.476
77.052
76.626
69.783
65.914
25.114
24.932
18.317
200
150
100
50
0
PPM

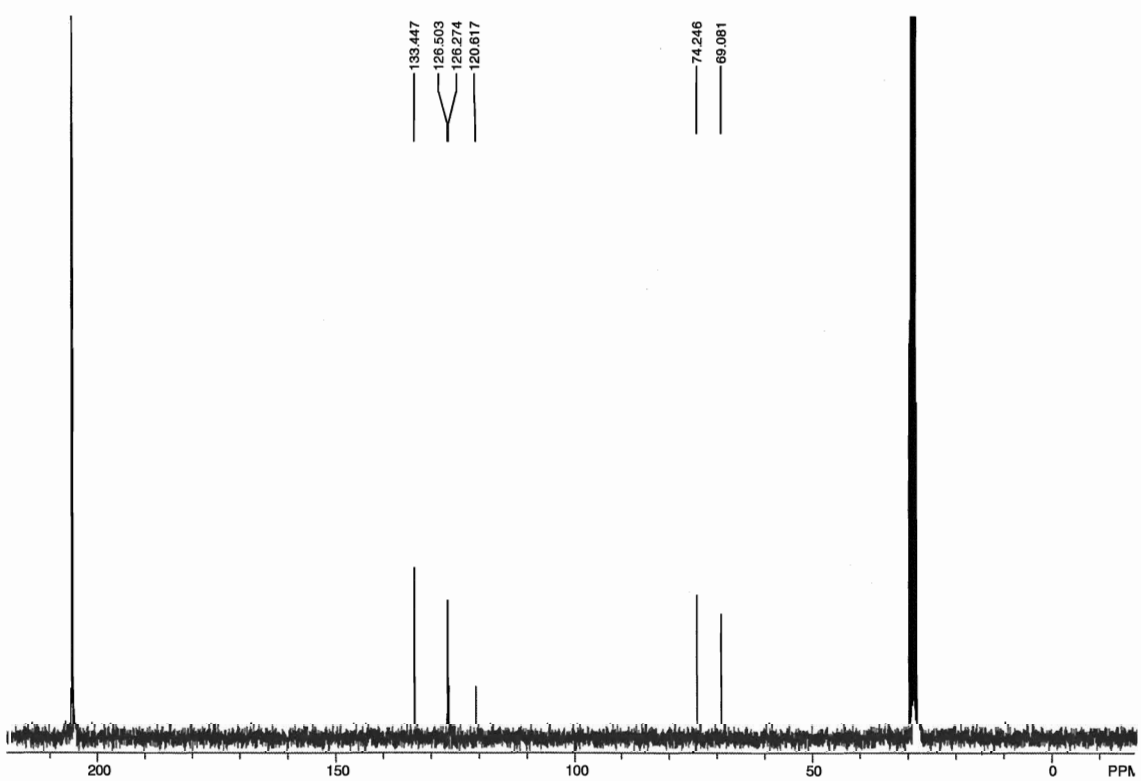

7.192
5.994
5.941
5.857
5.835
5.805
5.783
5.751
5.737
5.721
4.595
4.575
4.247
4.226
4.223
4.209
4.202
4.189
2.169
2.150
1.977
1.958
1.740
1.725
1.704
1.694
1.683
1.675
1.669
1.666
1.651
1.572
1.496
1.451
1.400
1.353
1.320
1.234
1.214
7.08
5.26
0.99
0.94
1.00
1.18
1.12
2.21
8
6
4
2
PPM

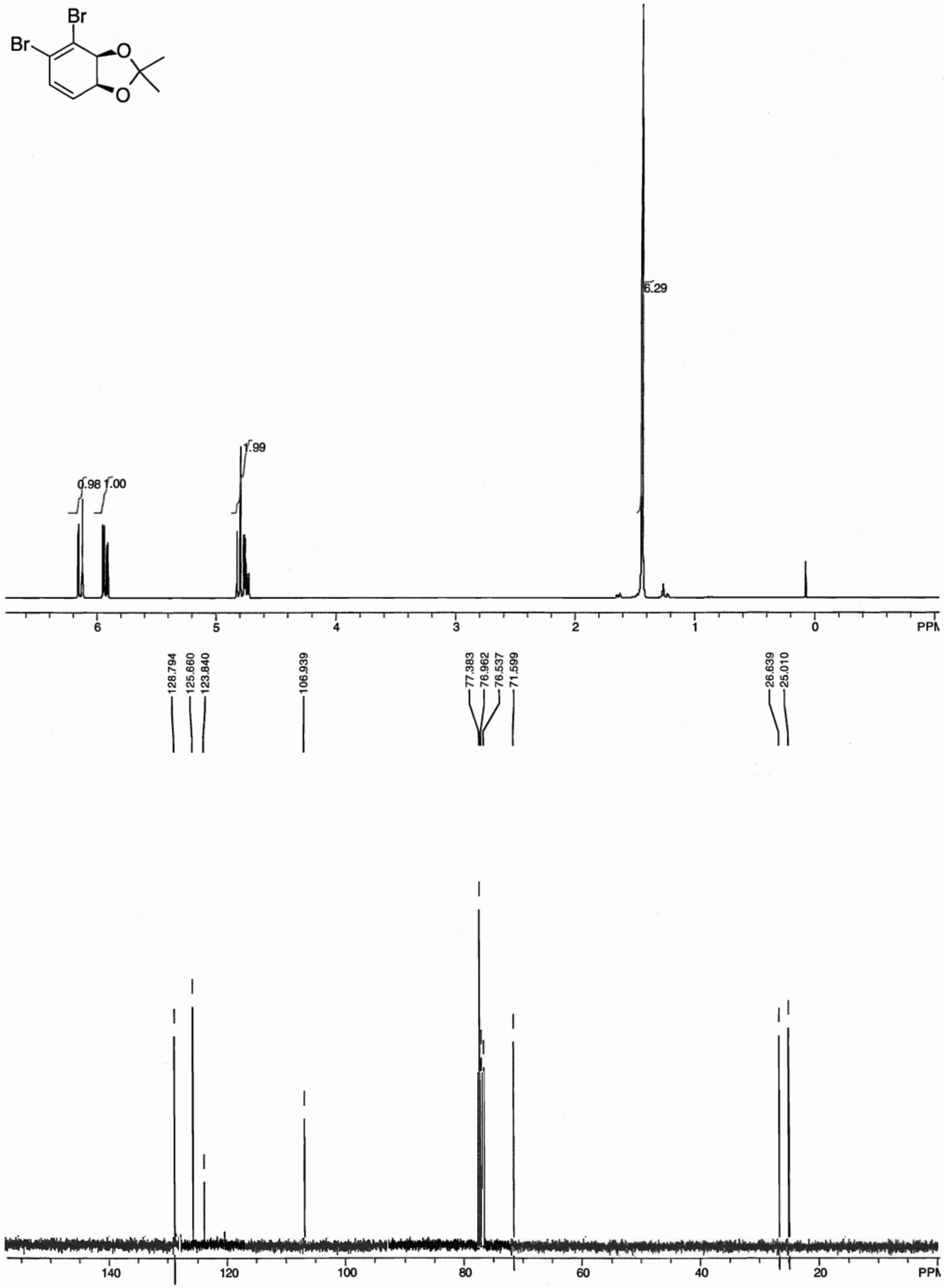

7.123
7.097
5.337
5.325
4.182
4.160
4.114
4.106
1.688
1.668
1.441
1.427
1.274
1.247
1.225
0.979
0.961
0.941
0.934
0.914
0.770
0.742
8.21
4.13
2.65
2.23
1.51
1.00
1.06
1.00
1.16
8
6
4
2
0
PPM

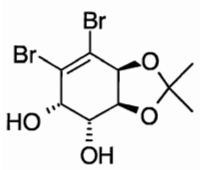


in acetone d_6

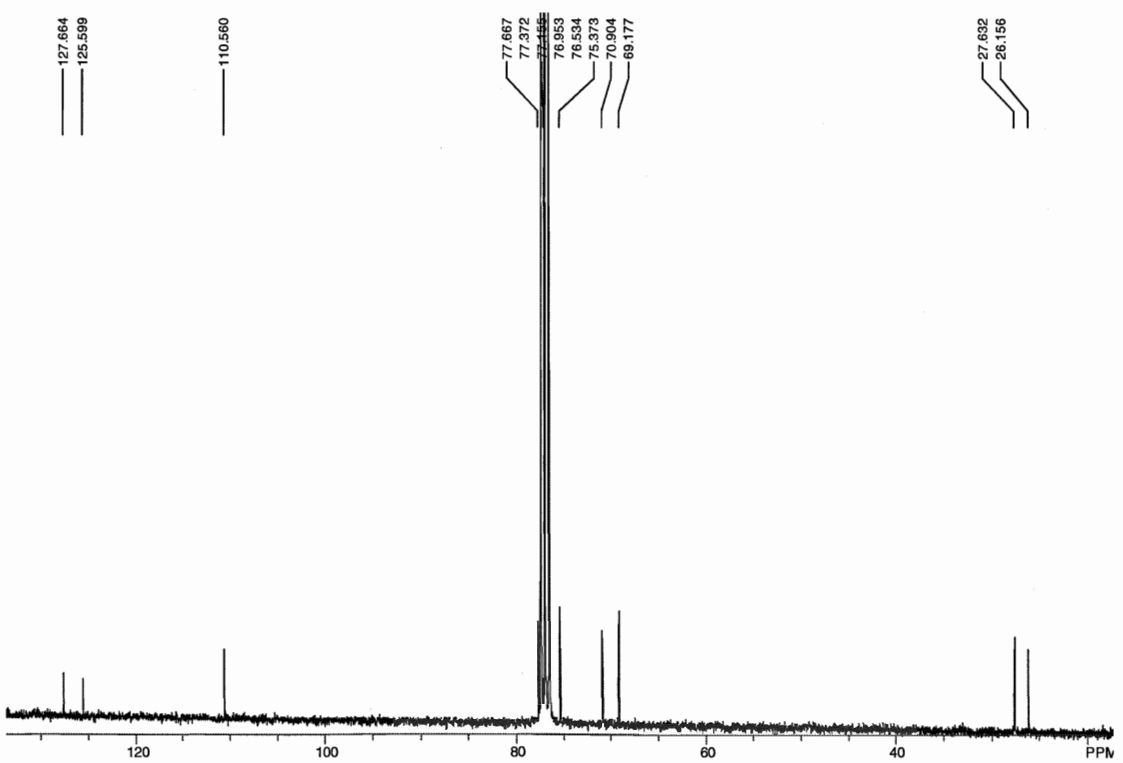


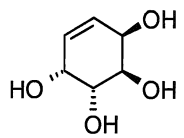



Br
Br
O
O
6.29
1.99
0.98
1.00
6
5
4
3
2
1
0
PPM
128.794
125.660
123.840
106.939
77.383
76.962
76.537
71.599
26.639
25.010
140
120
100
80
60
40
20
PPM


Br
Br
O
O
HO
OH

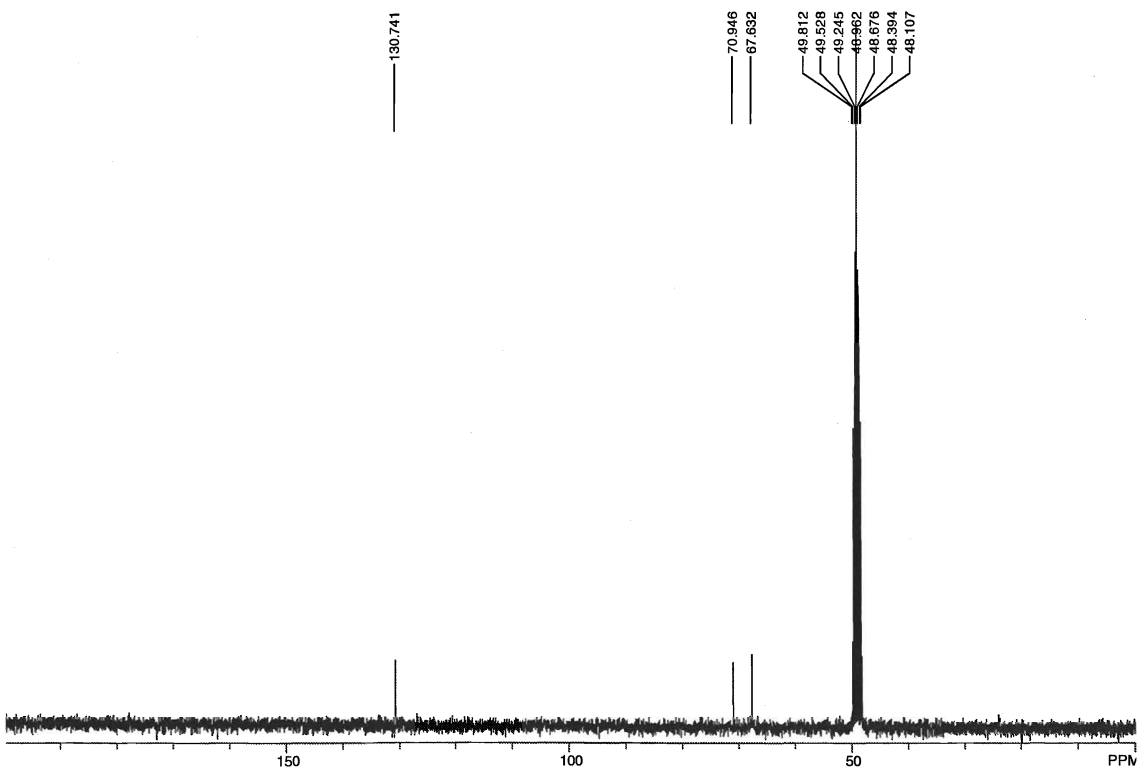
7.278
4.483
4.466
4.454
4.450
4.357
1.486
10
8
6
4
2
PPM

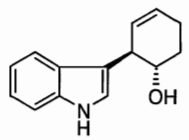

127.664
125.599
110.560
77.667
77.372
76.953
76.534
75.373
70.904
69.177
27.632
26.156
120
100
80
60
40
PPM

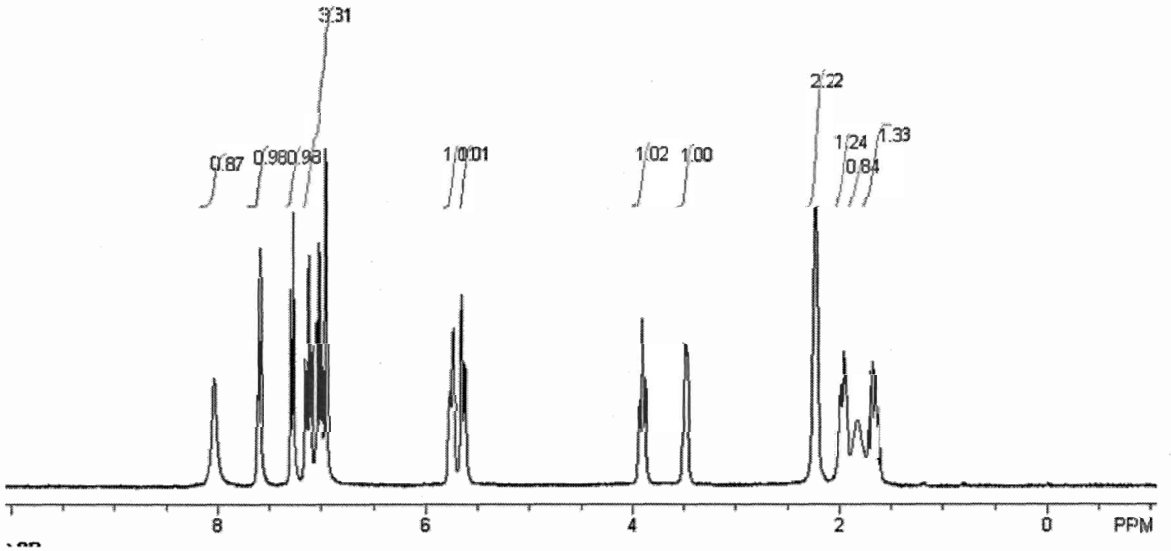

OH
HO
OH
OH

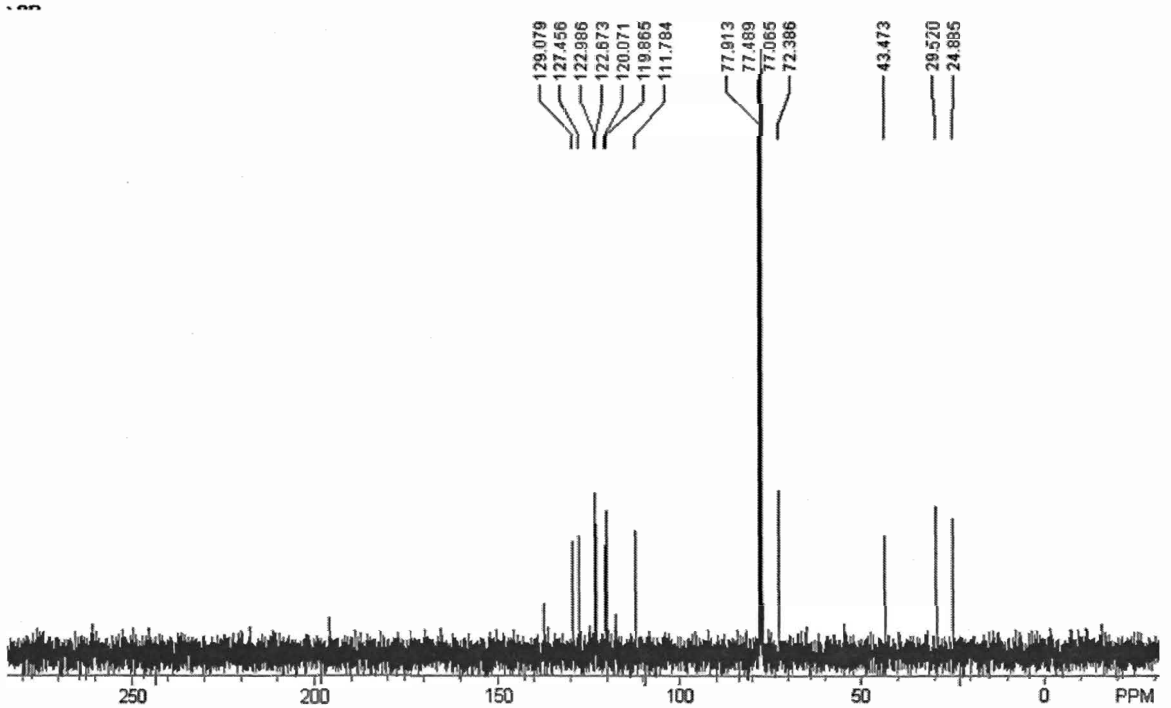
in MeOD

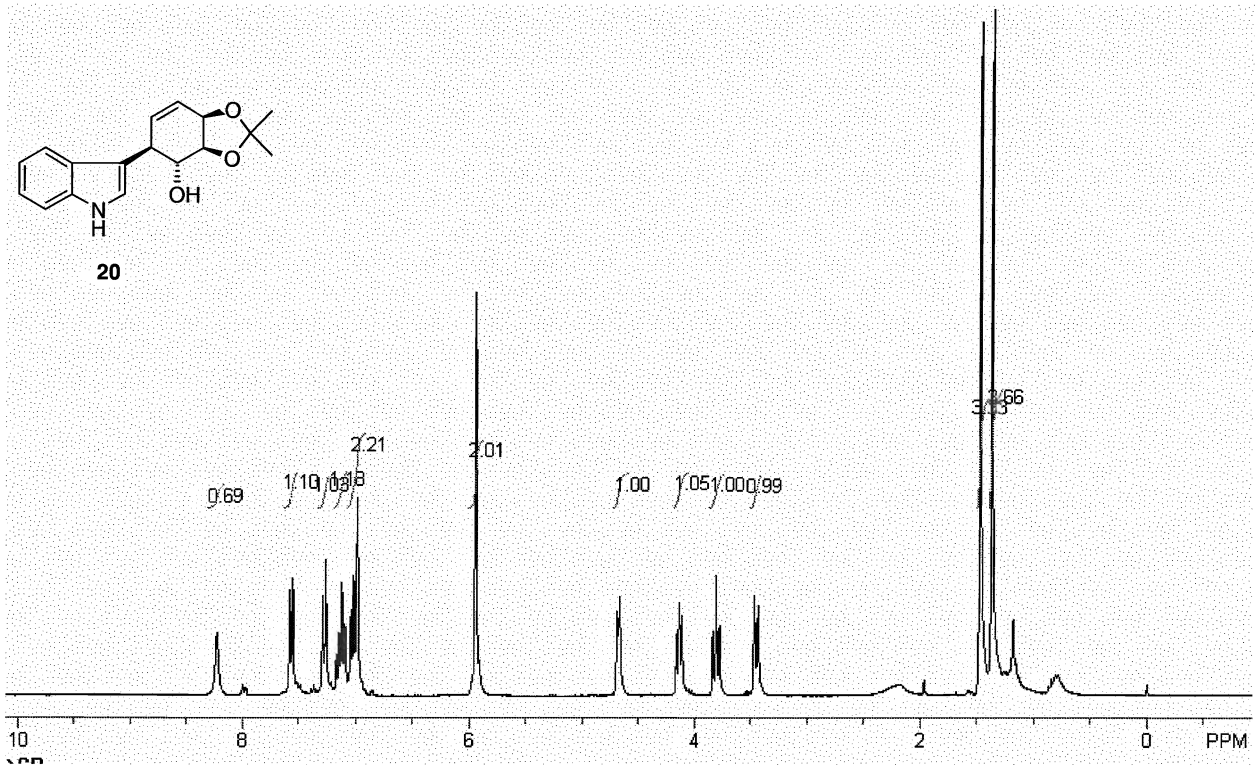
5.801
5.795
4.850
4.269
3.935
3.932
3.929
3.924
1.01
0.99
1.00
10
8
6
4
2
PPM

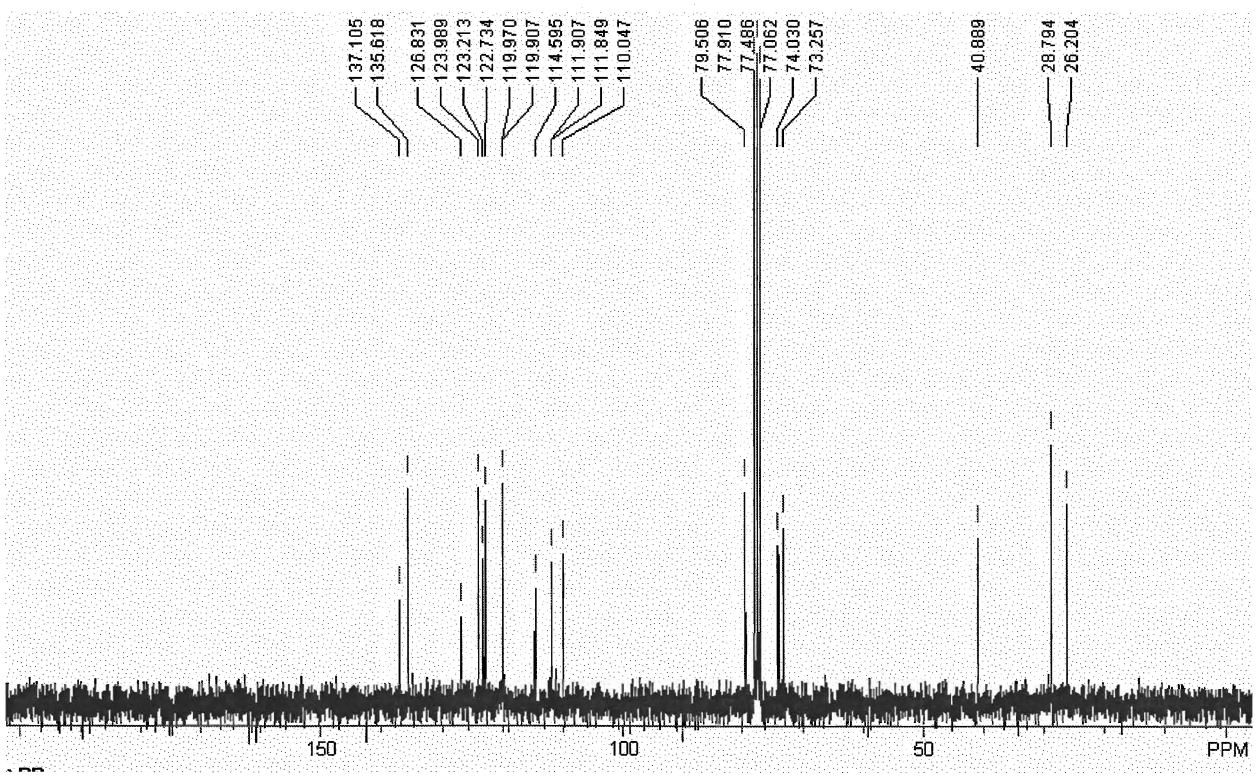

130.741
70.946
67.632
49.812
49.528
49.245
48.962
48.676
48.394
48.107
150
100
50
PPM

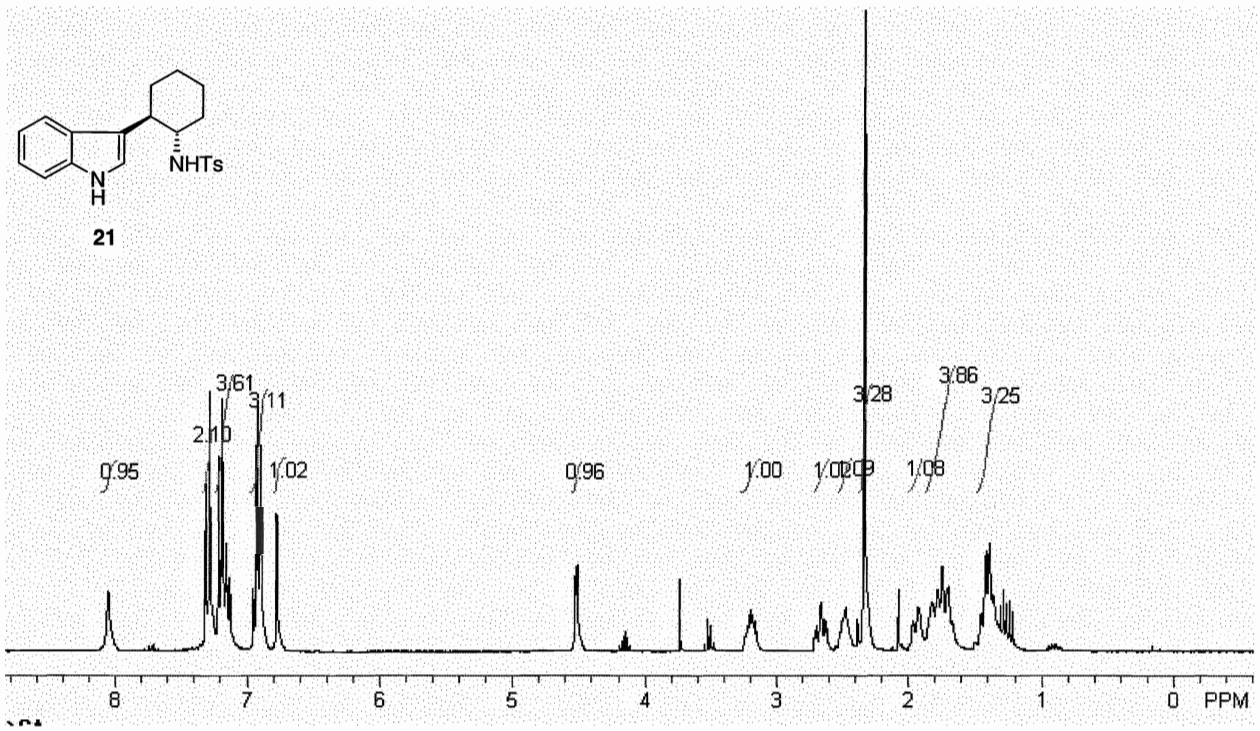

OH
N
H

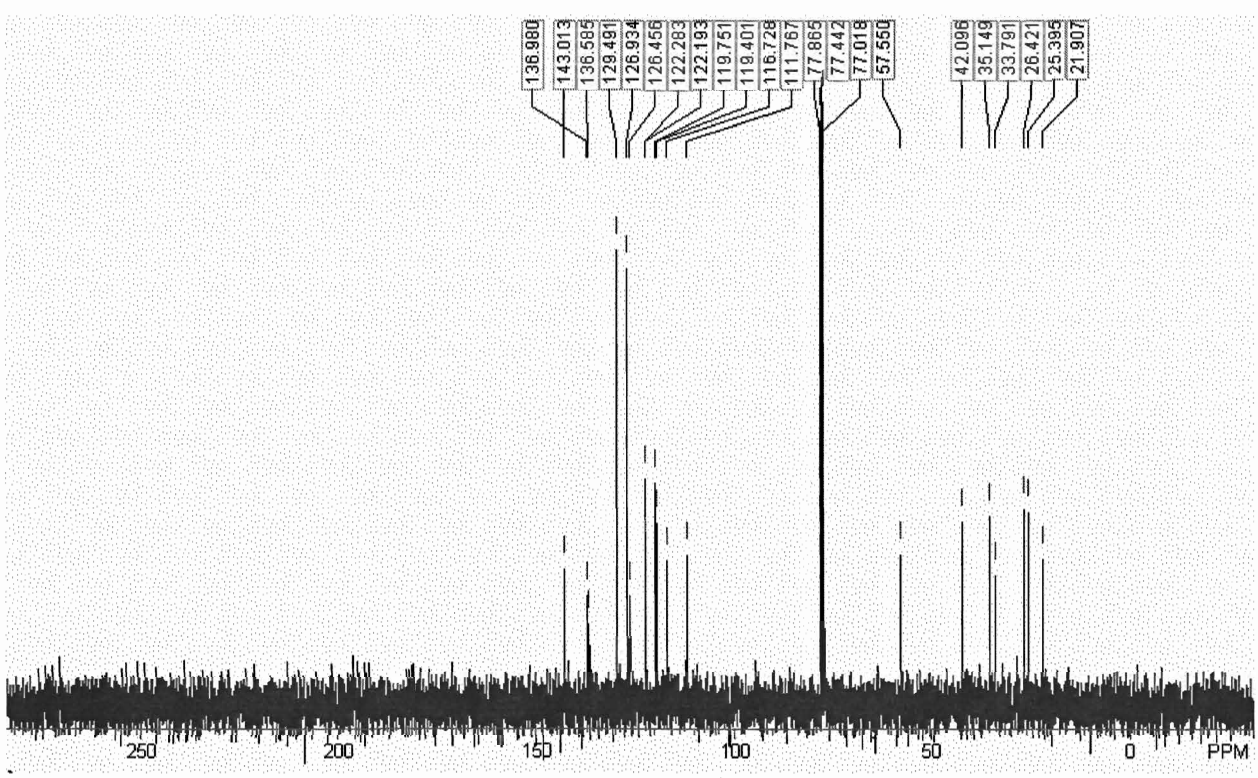

3.31
2.22
0.87
0.98
0.98
1.01
1.02
1.00
1.24
1.33
0.84
8
6
4
2
0
PPM

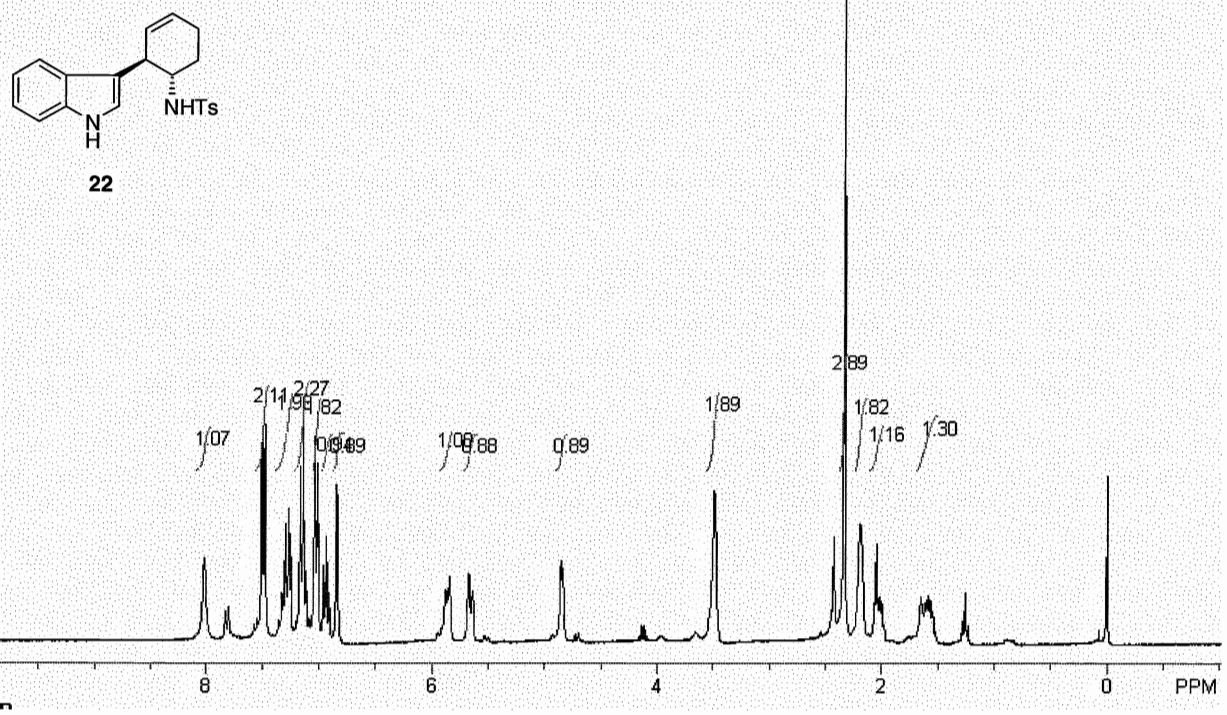

129.079
127.456
122.986
122.673
120.071
119.865
111.784
77.913
77.489
77.065
72.386
43.473
29.520
24.885
250
200
150
100
50
0
PPM

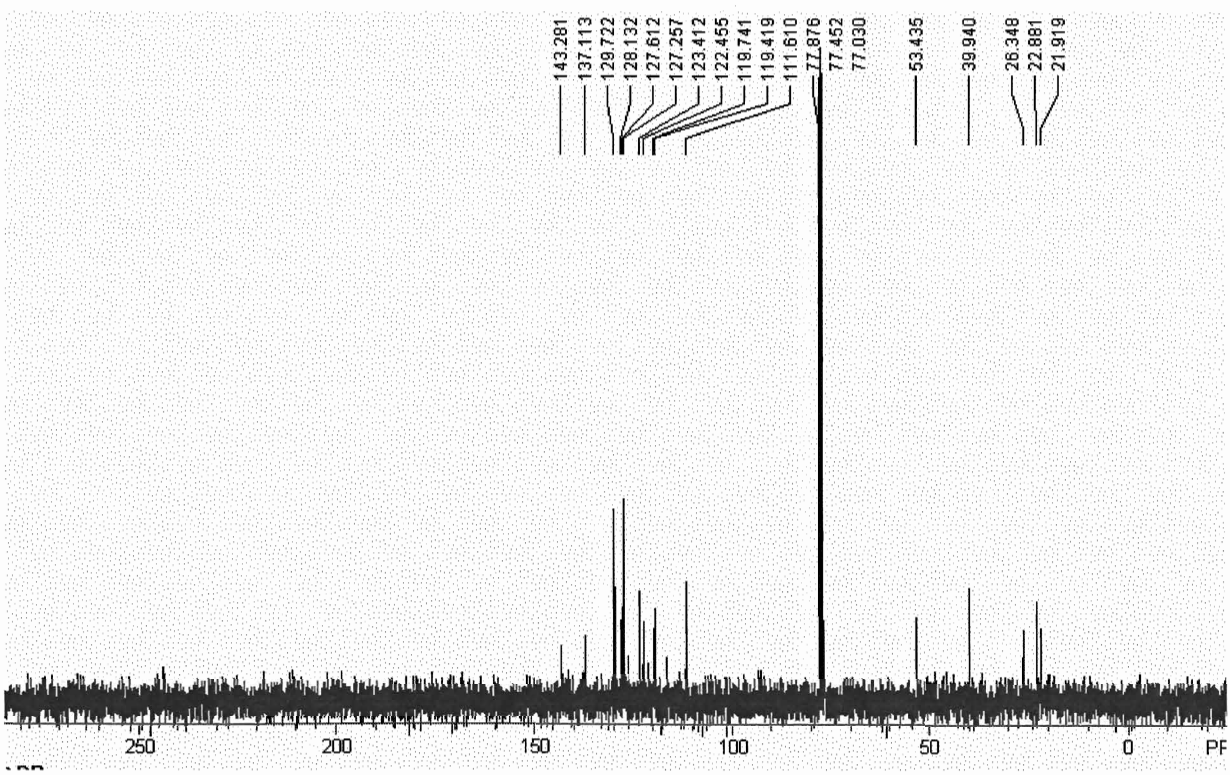

O
O
OH
N
H
20
0.69
1.10
1.03
2.21
2.01
1.00
1.05
1.00
0.99
3.66
10
8
6
4
2
0
PPM

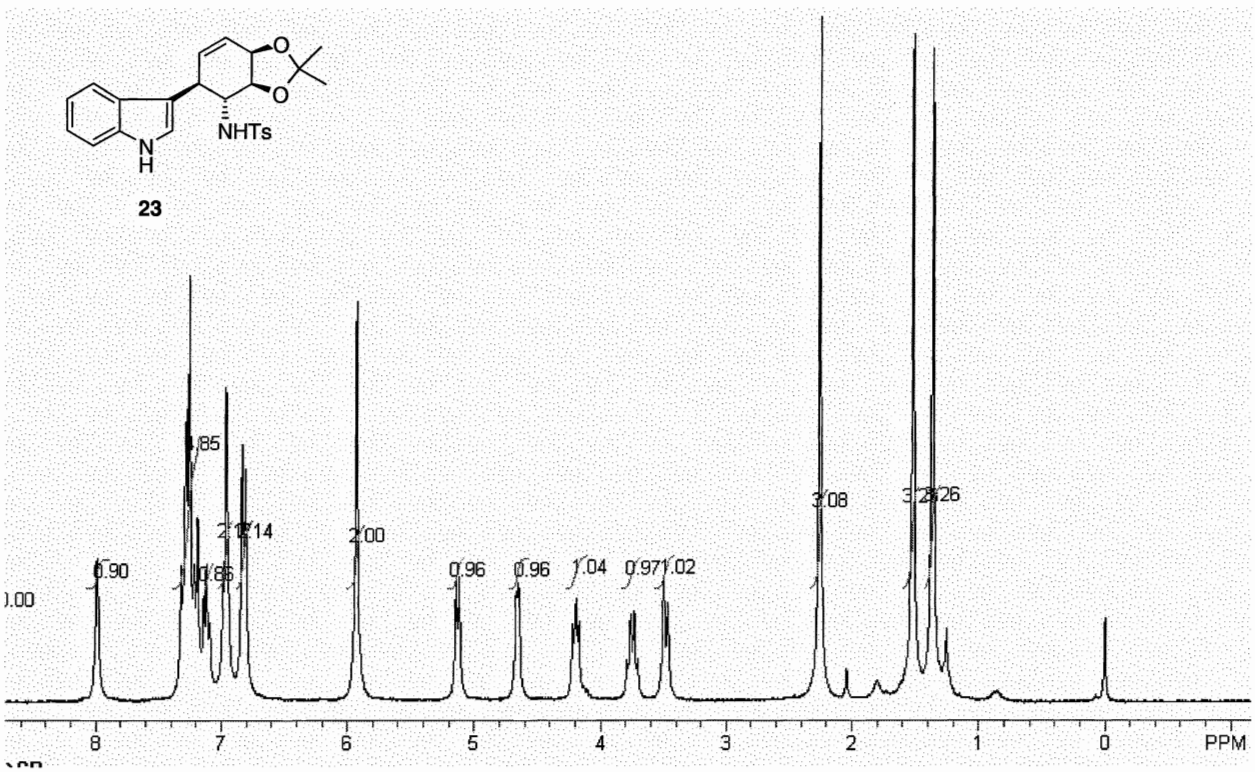

137.105
135.618
126.831
123.989
123.213
122.734
119.970
119.907
114.595
111.907
111.849
110.047
79.506
77.910
77.486
77.062
74.030
73.257
40.889
28.794
26.204
150
100
50
PPM

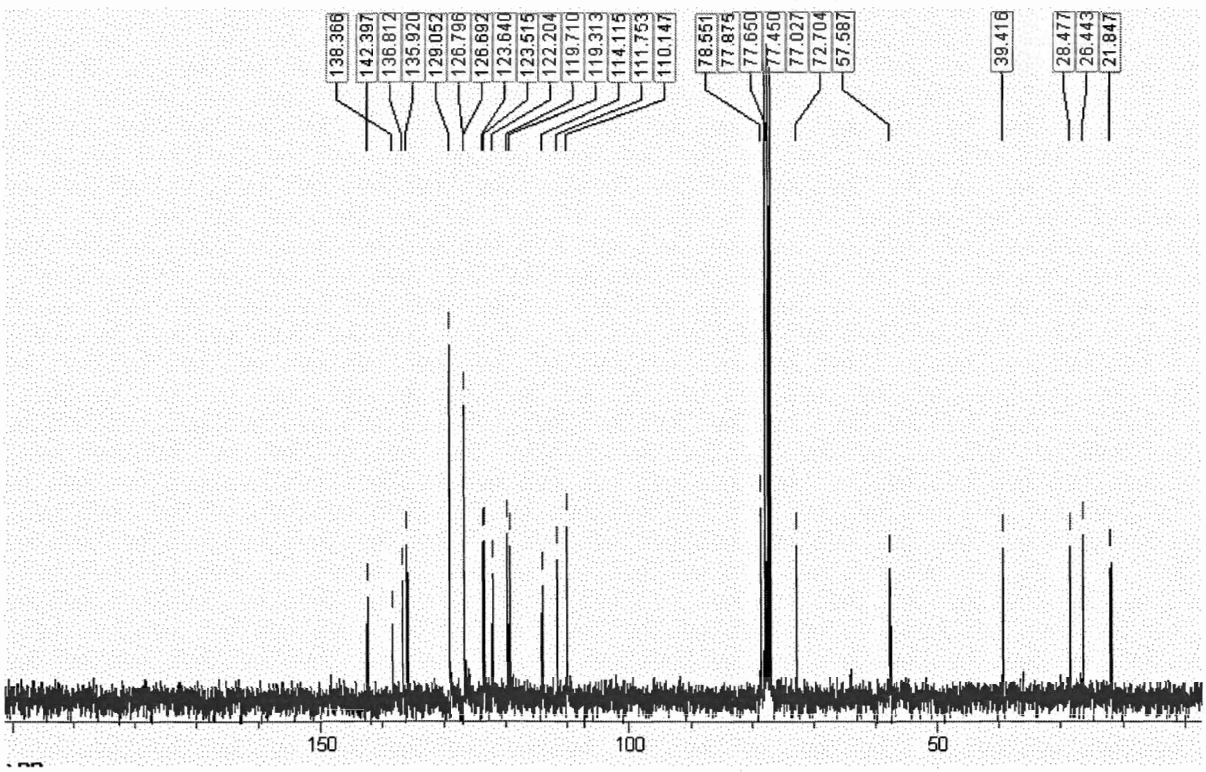

NHTs
N
H
21
3.61
3.11
2.10
0.95
1.02
0.96
1.00
3.28
3.86
3.25
1.08
8
7
6
5
4
3
2
1
0
PPM


136.980
143.013
136.585
129.491
126.934
126.456
122.283
122.193
119.751
118.401
116.728
111.767
77.865
77.442
77.018
57.550
42.096
35.149
33.791
26.421
25.395
21.907
250
200
150
100
50
0
PPM


NHTs
N
H
22
2.89
2.11
2.27
1.98
1.82
1.07
1.89
1.82
1.16
1.30
1.08
0.88
0.89
8
6
4
2
0
PPM


143.281
137.113
129.722
128.132
127.612
127.257
123.412
122.455
118.741
119.419
111.610
77.876
77.452
77.030
53.435
39.940
26.348
22.881
21.919
250
200
150
100
50
0
PP


NHTs
H
23
0.90
0.85
2.00
0.96
0.96
1.04
0.97
1.02
3.08
8
7
6
5
4
3
2
1
0
PPM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100
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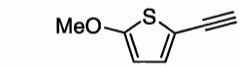
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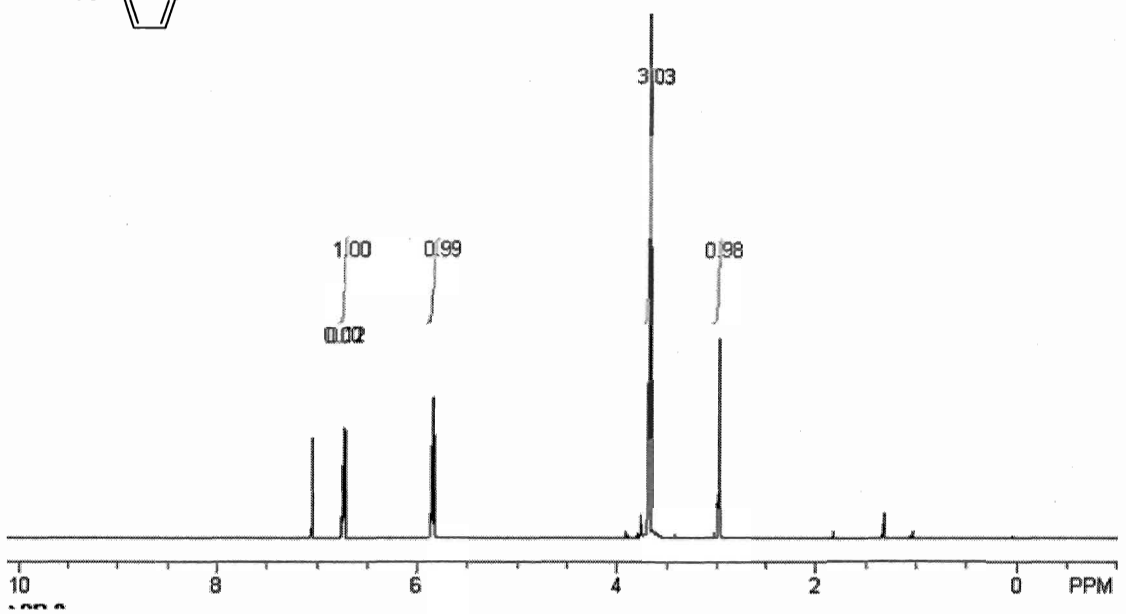
S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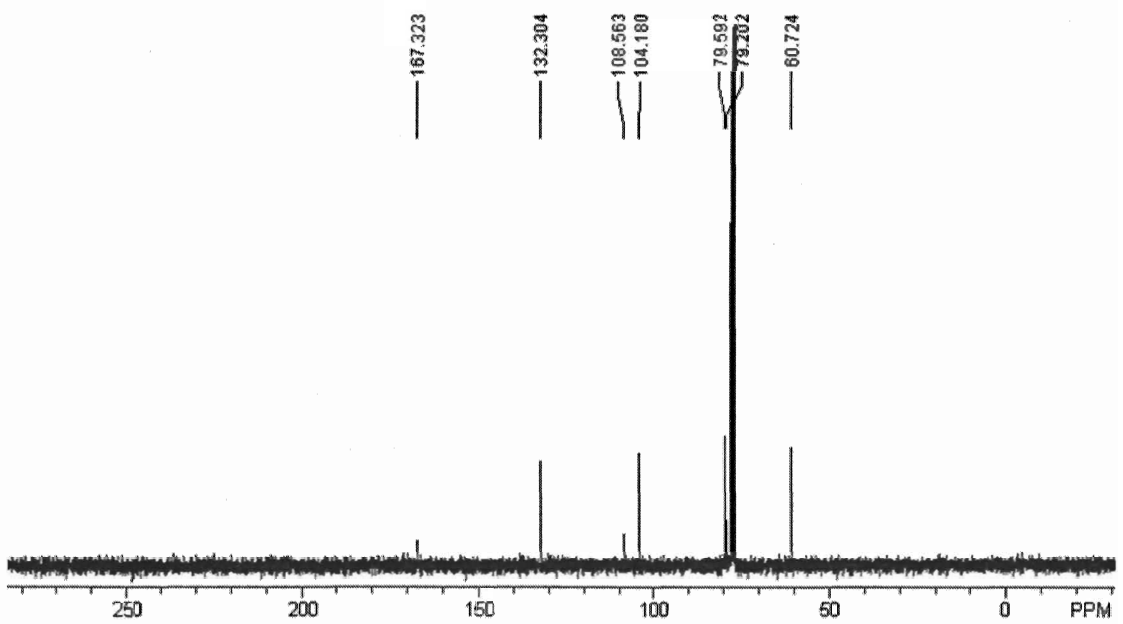
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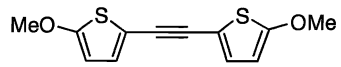
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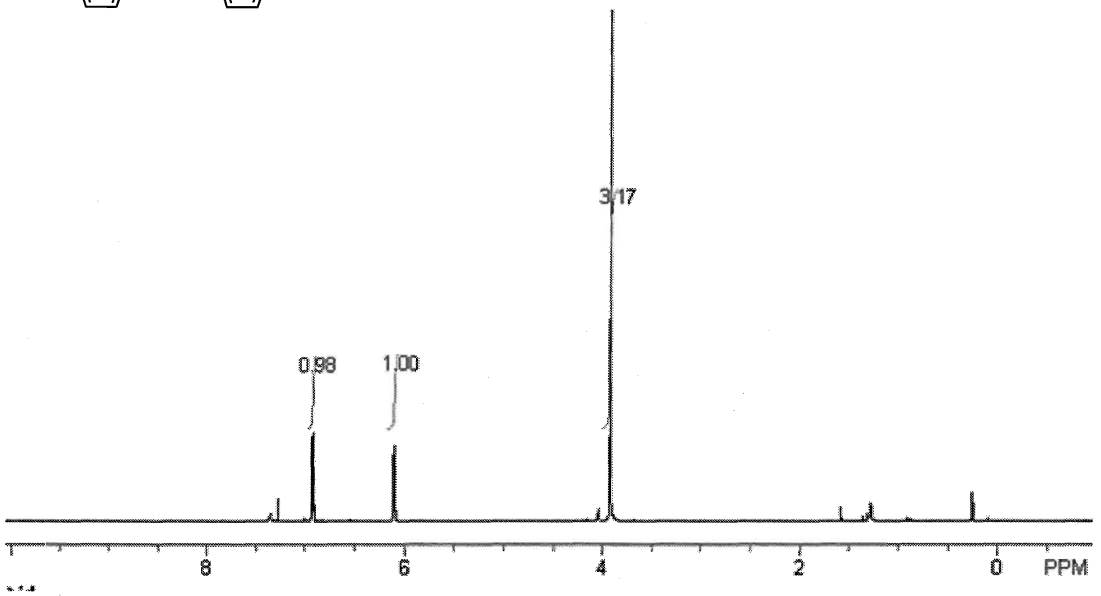
S
S
OMe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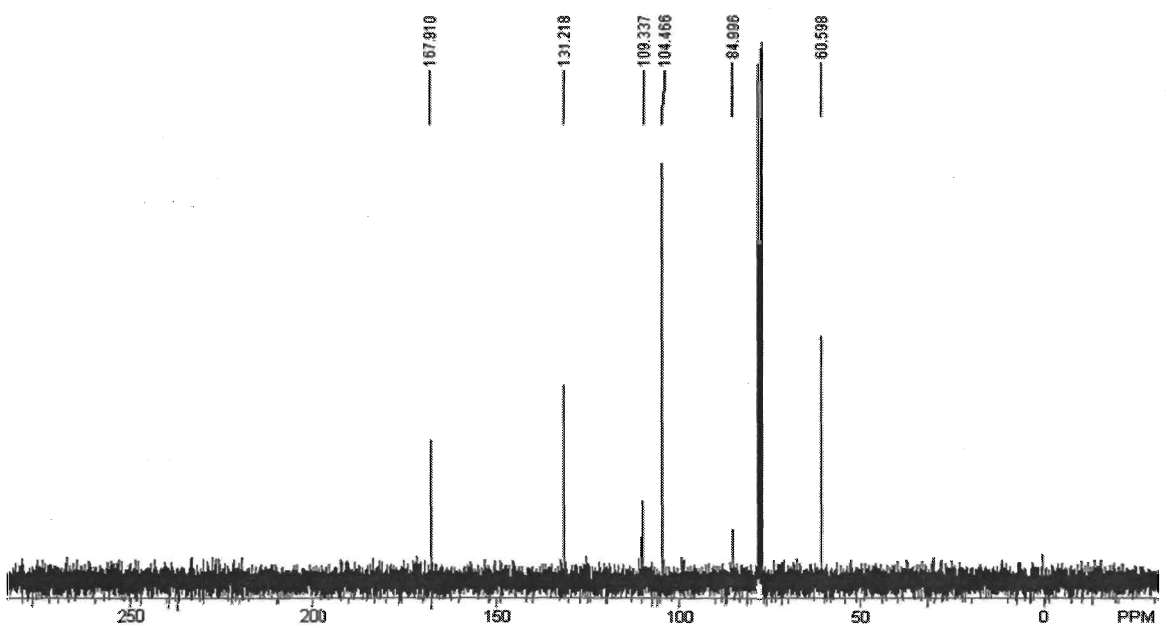
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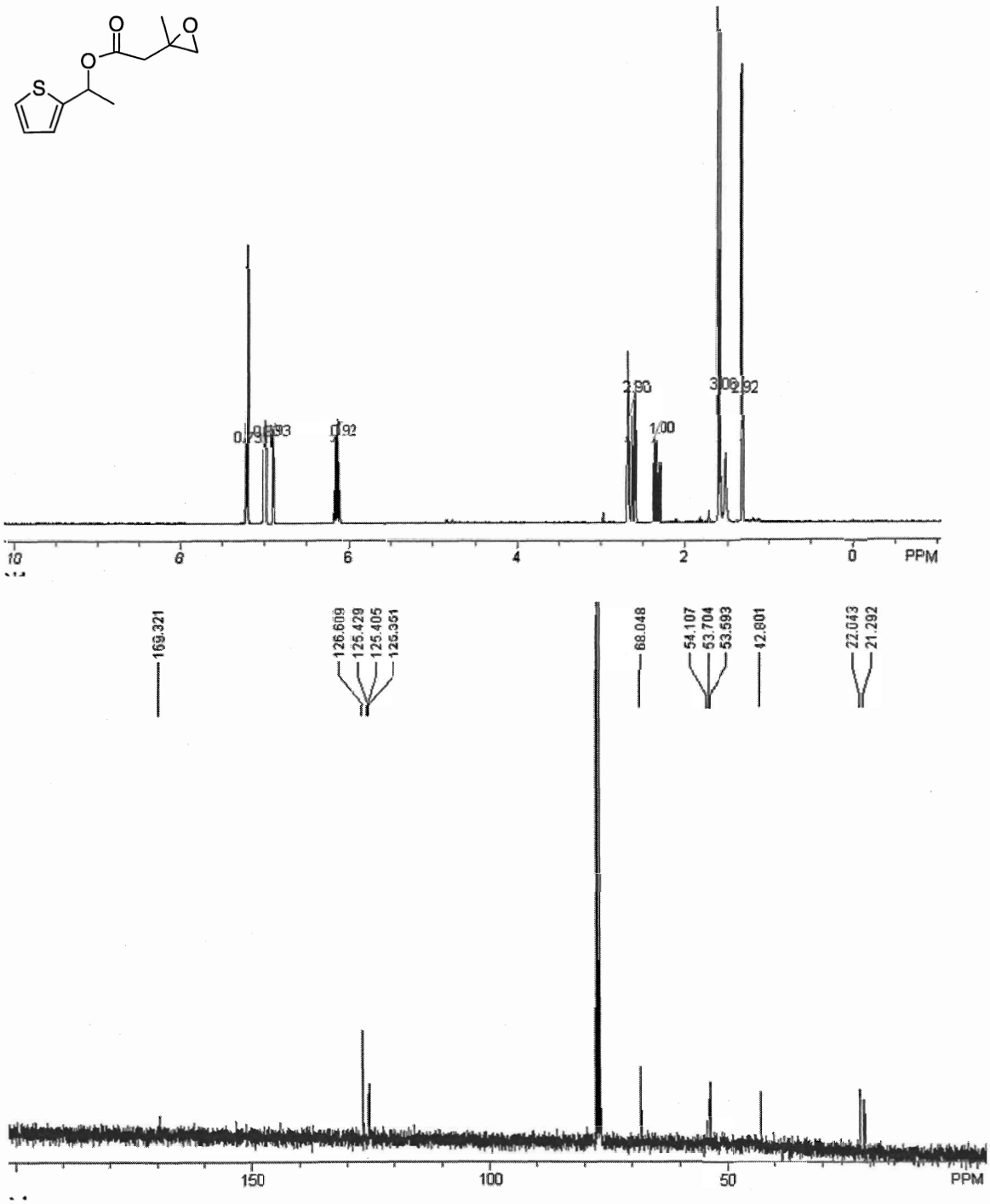
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O
O
S
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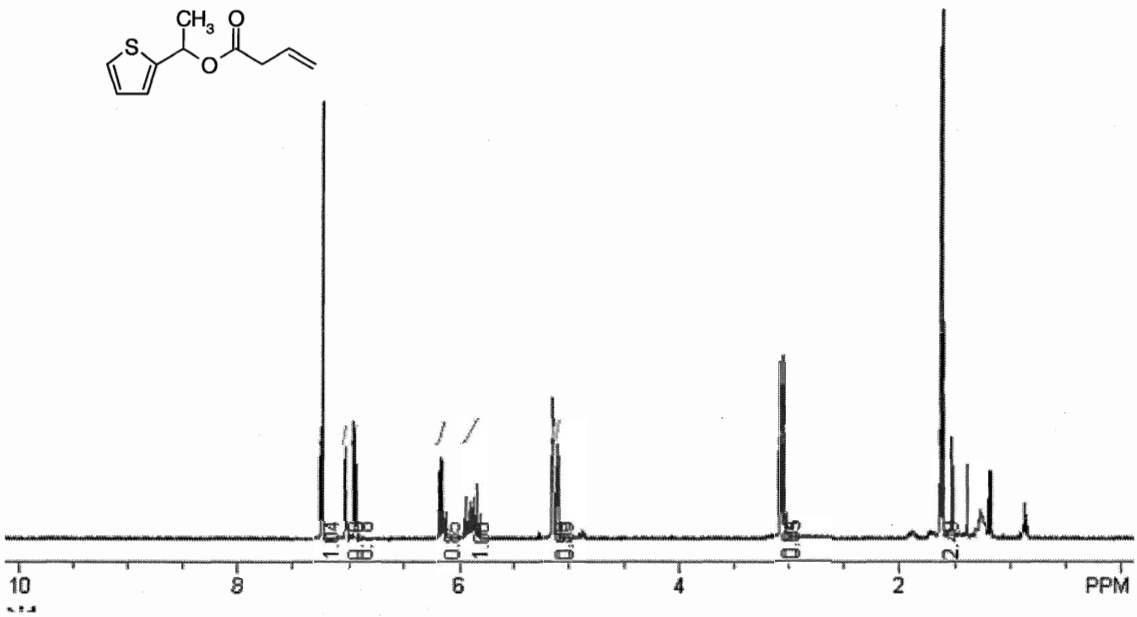
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S
O
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6
4
2
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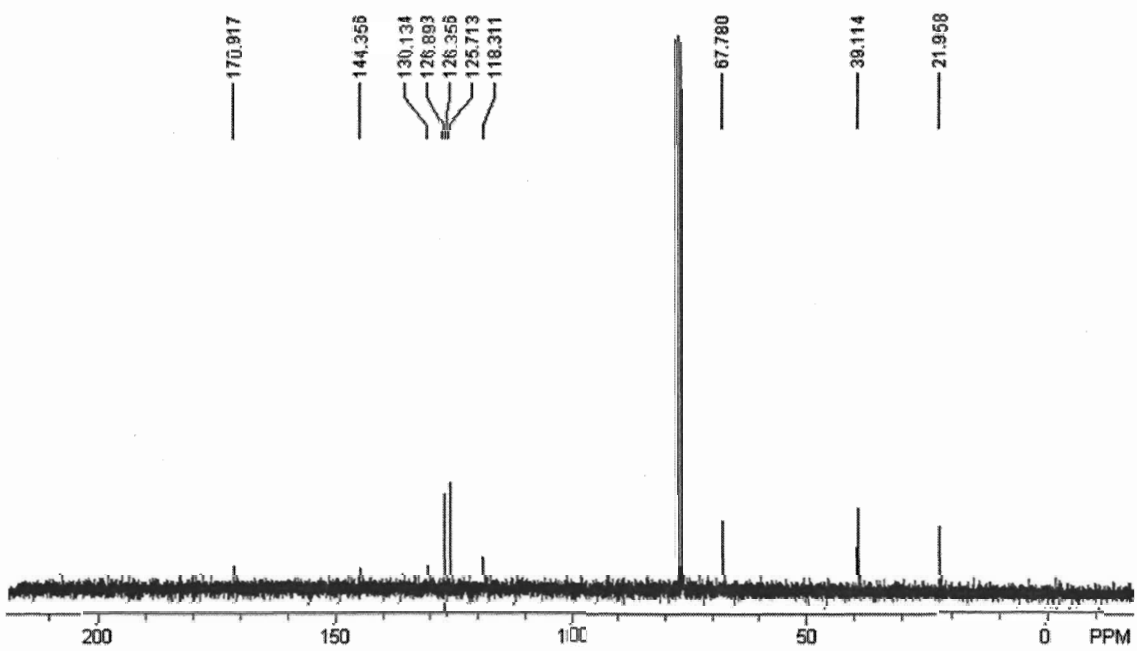
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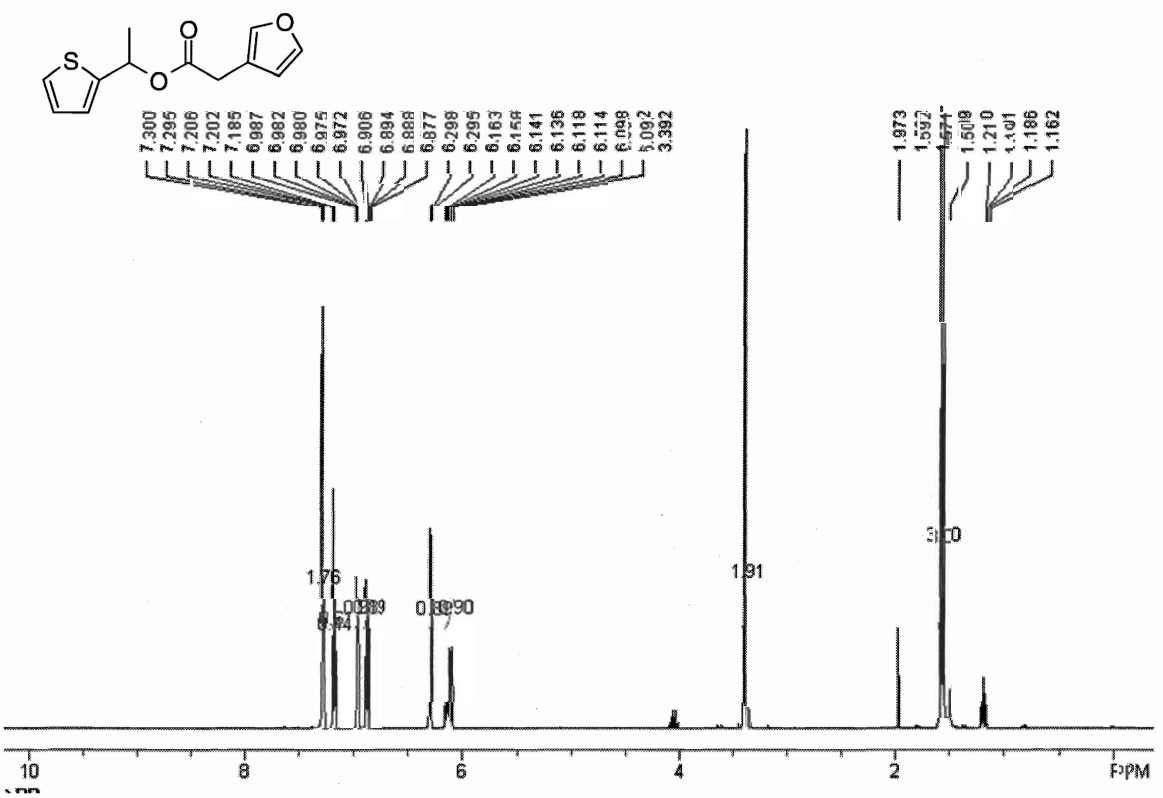
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6.894
6.888
6.877
6.298
6.295
6.163
6.158
6.141
6.136
6.118
6.114
6.098
5.092
3.392
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1.509
1.210
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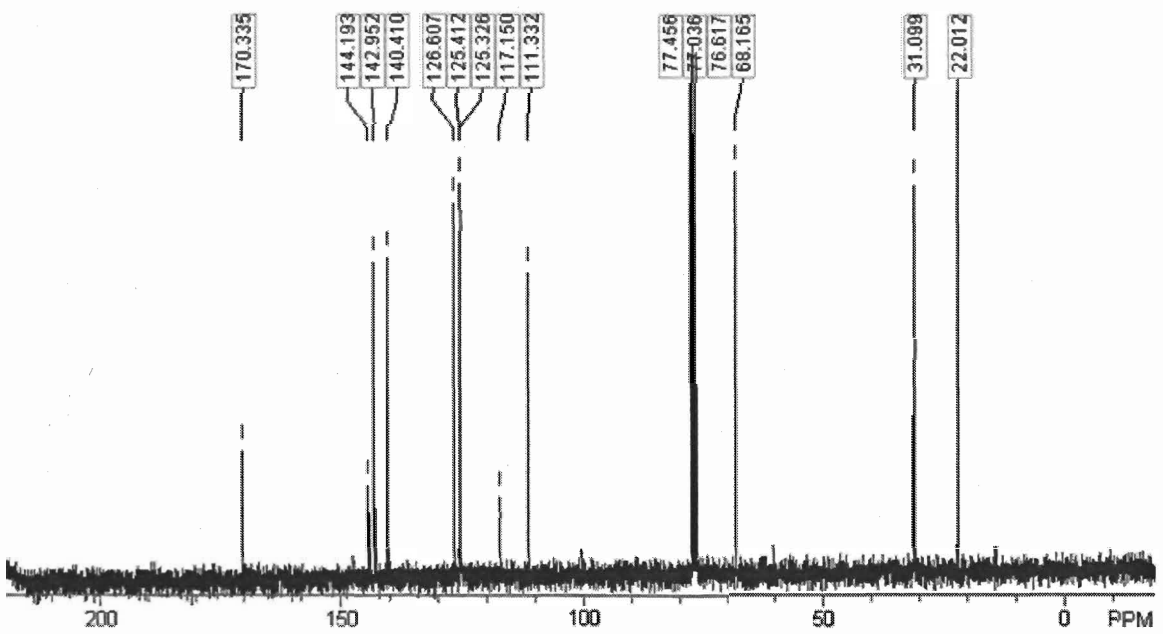
1.162
1.76
1.91
10
8
6
4
2
PPM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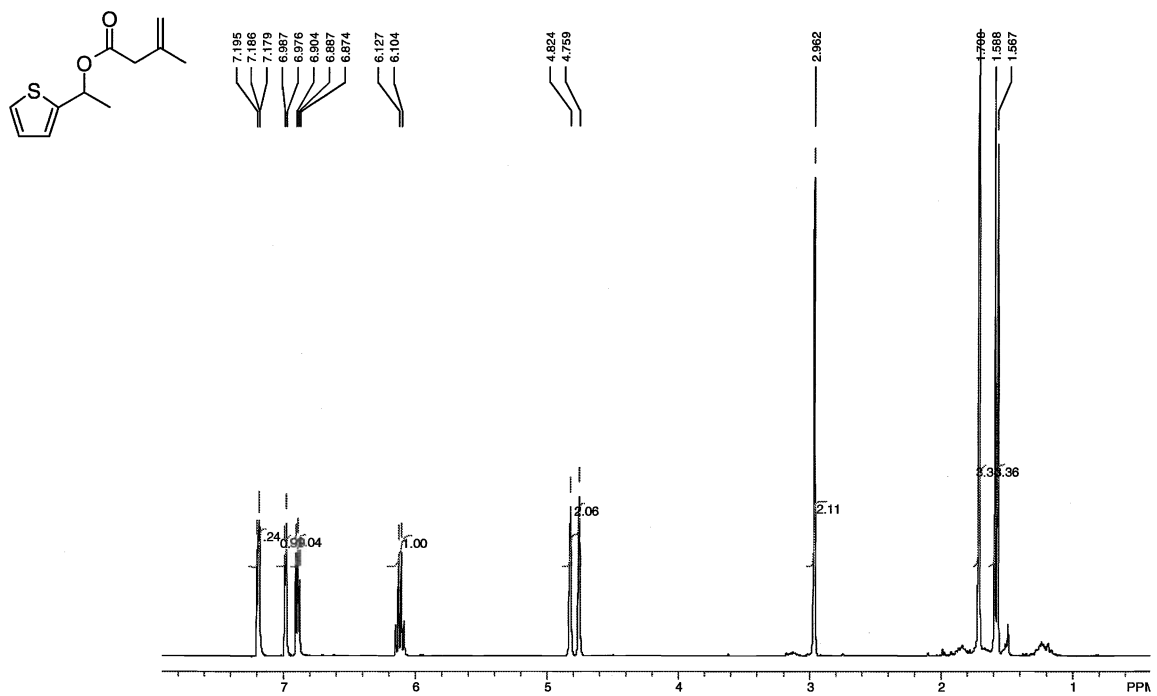
PPM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6.104
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4.759
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1.798
1.588
1.567
1.24
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1.00
2.06
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6
5
4
3
2
1
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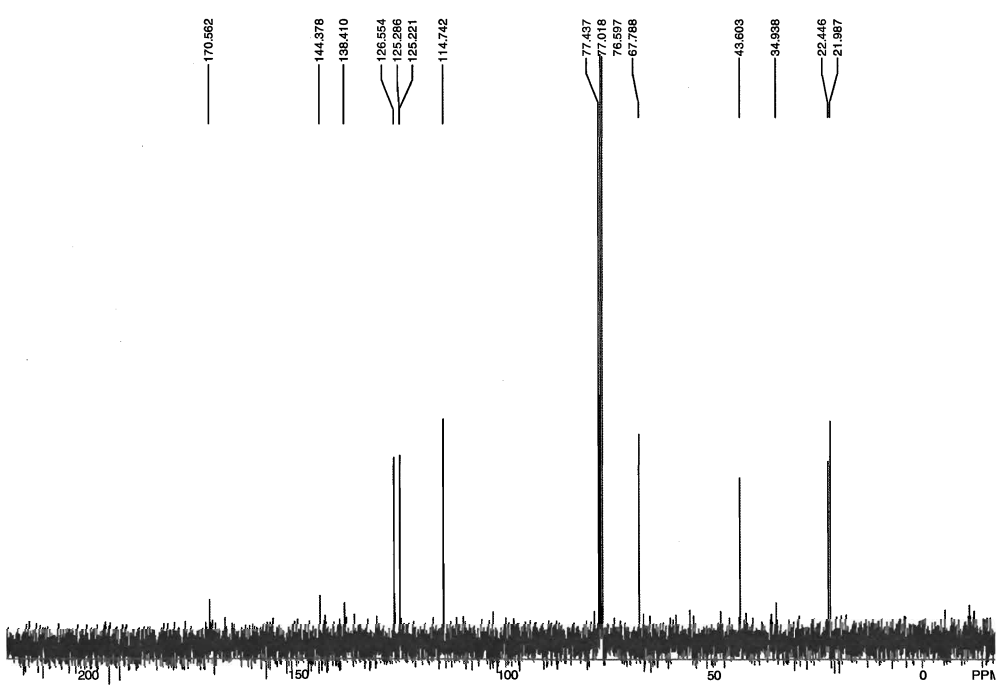
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0
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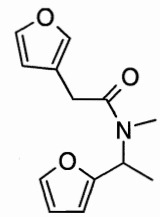

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6
4
2
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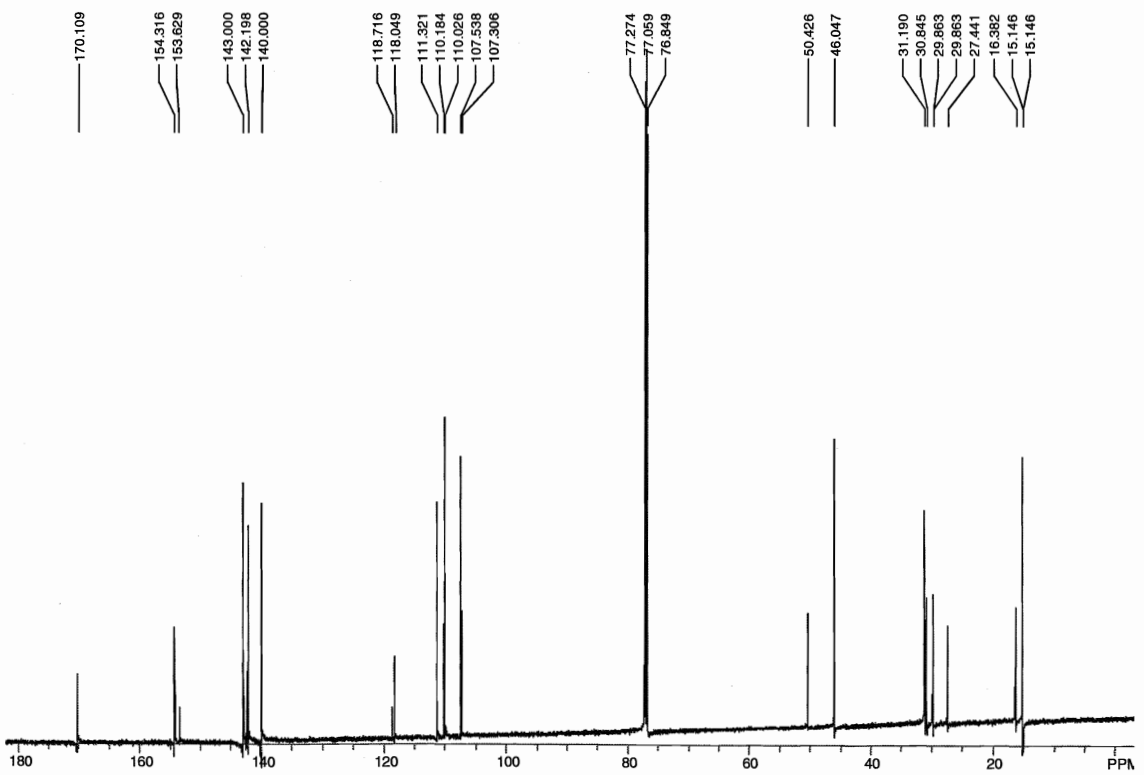
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50.426
46.047
31.190
30.845
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15.146
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140
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60
40
20
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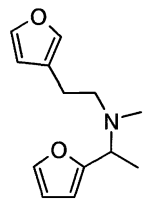

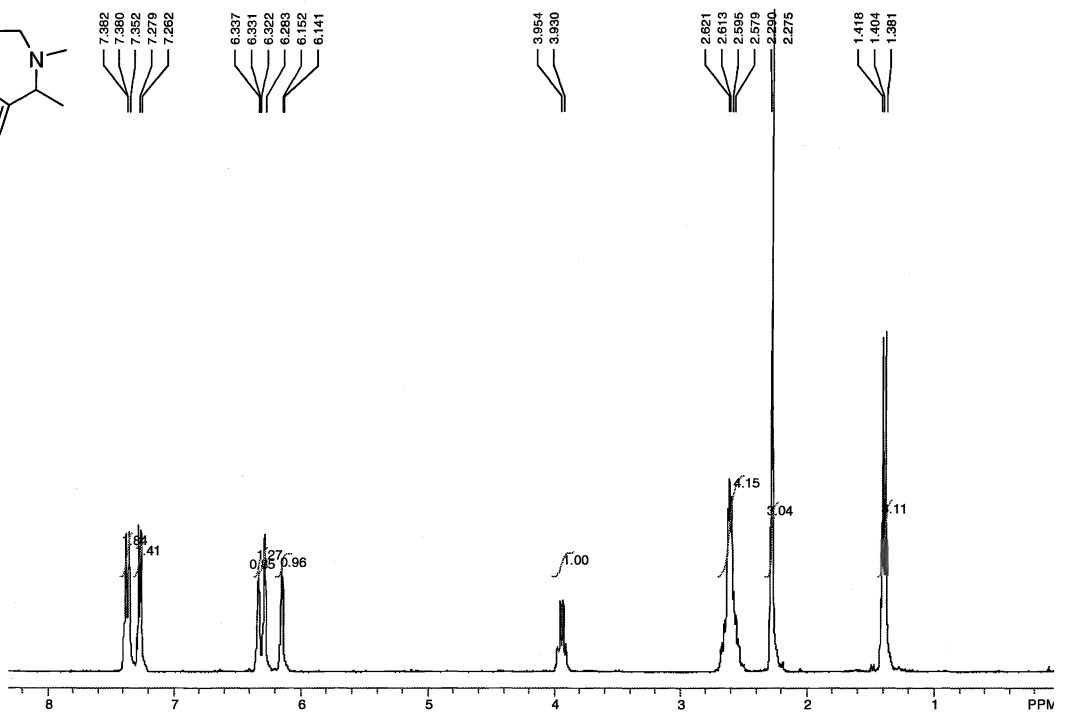
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6.141
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3.930
2.621
2.613
2.595
2.579
2.290
2.275
1.418
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3.04
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7
6
5
4
3
2
1
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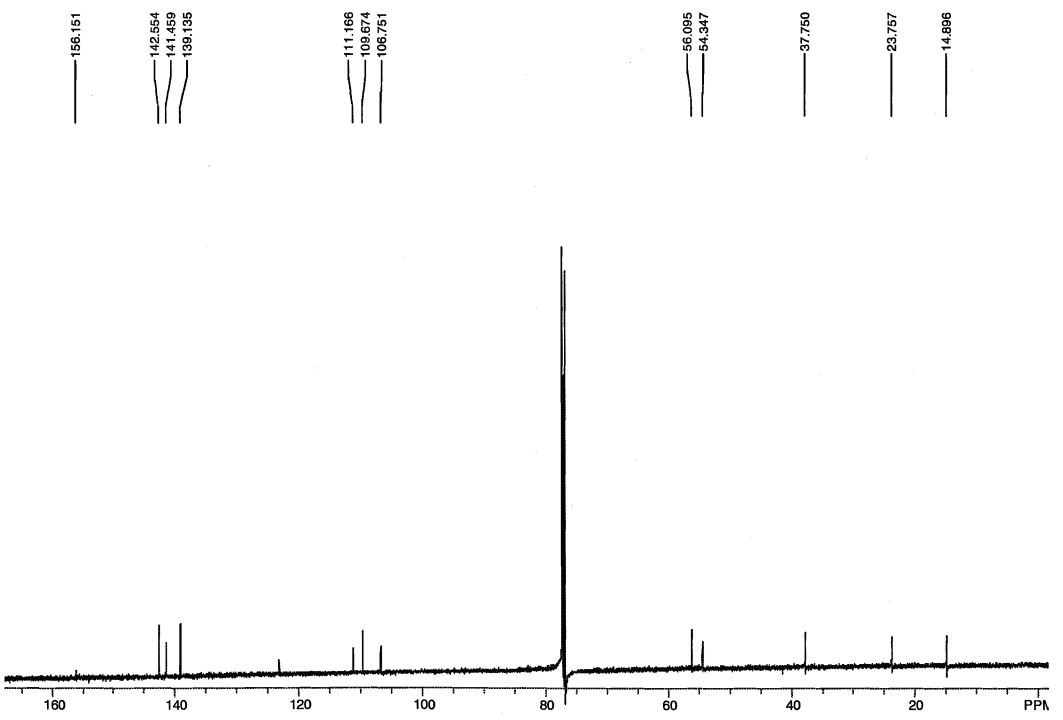
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140
120
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80
60
40
20
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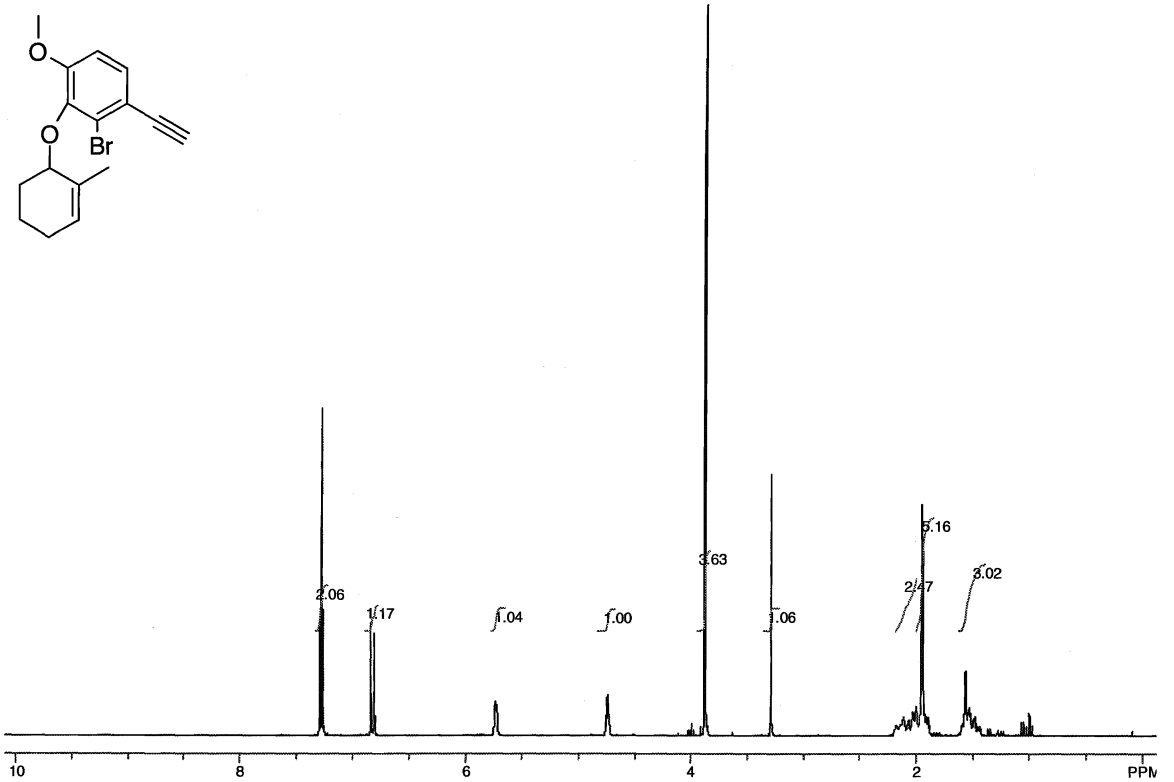
O
O
Br
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1.04
1.00
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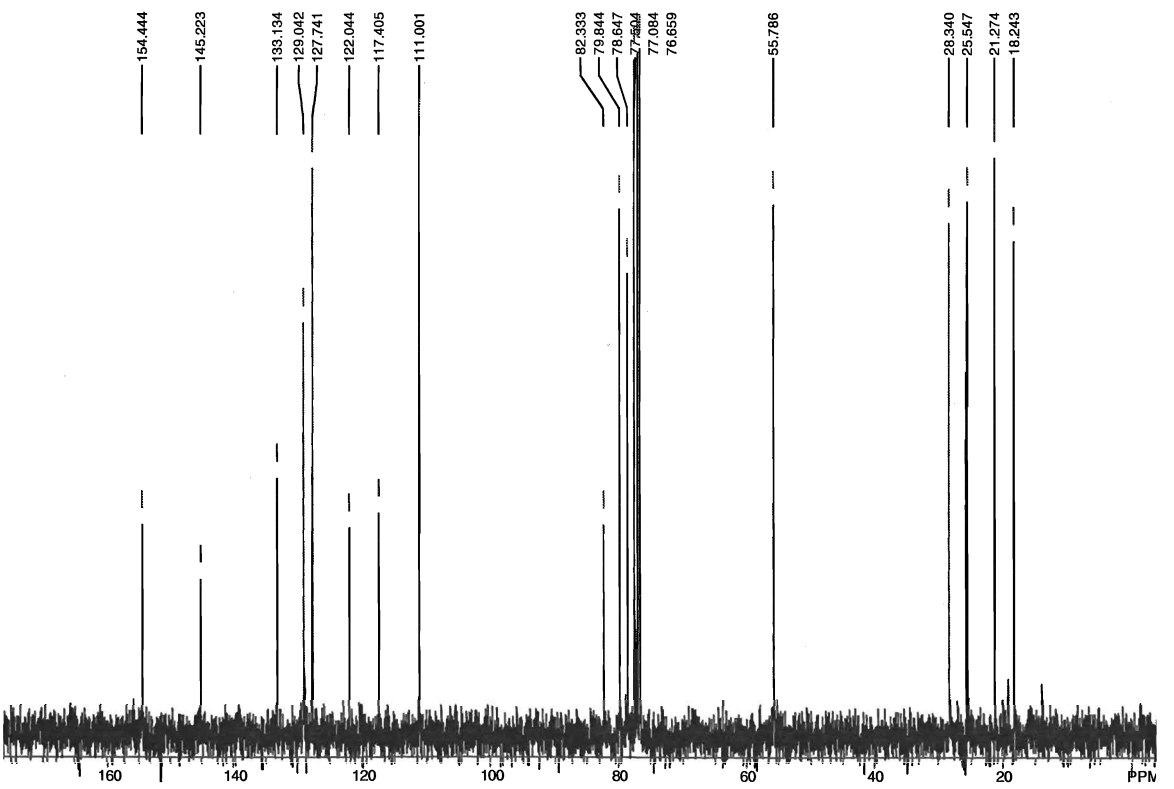
1.06
5.16
2.47
3.02
10
8
6
4
2
PPM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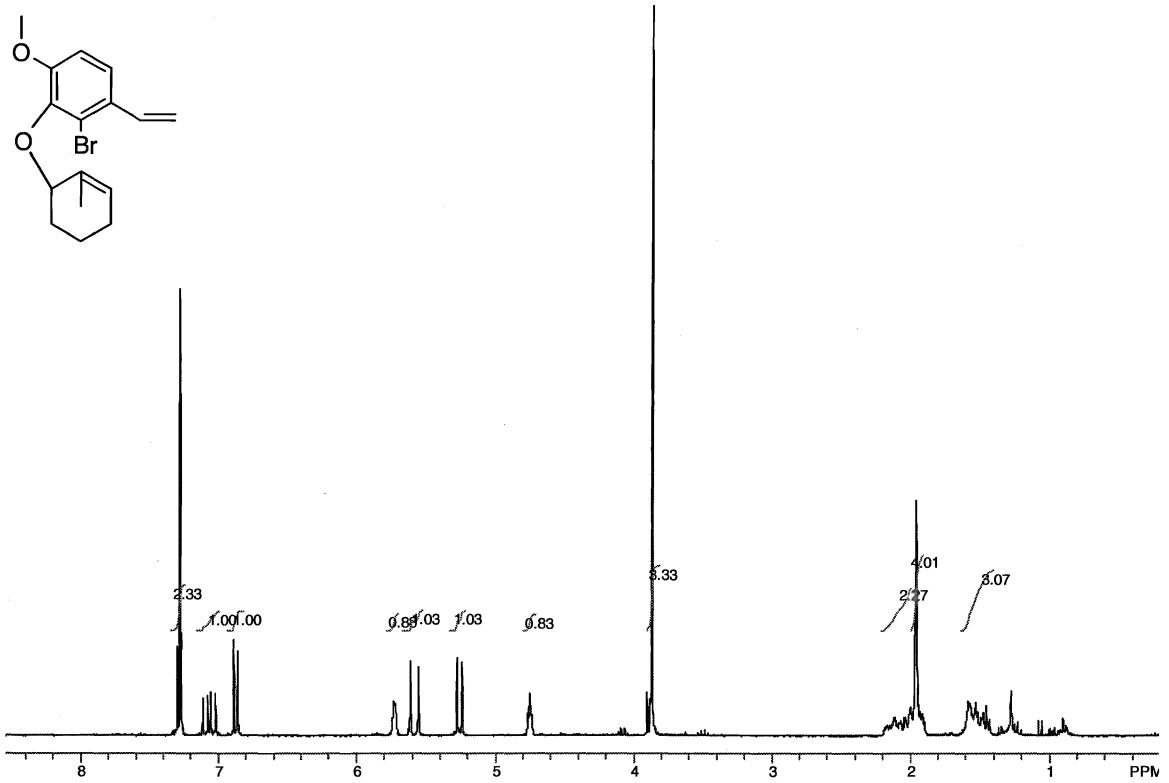
40
20
PPM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O
Br
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1.00
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7
6
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4
3
2
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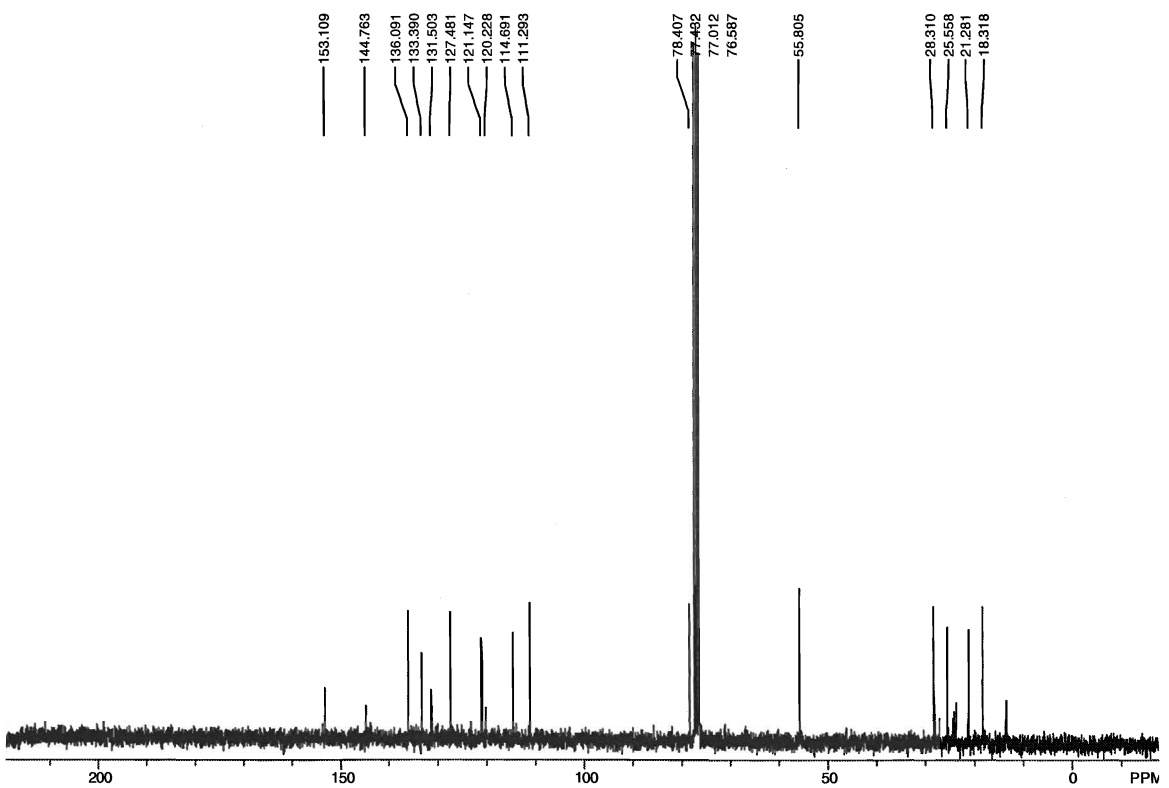
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50
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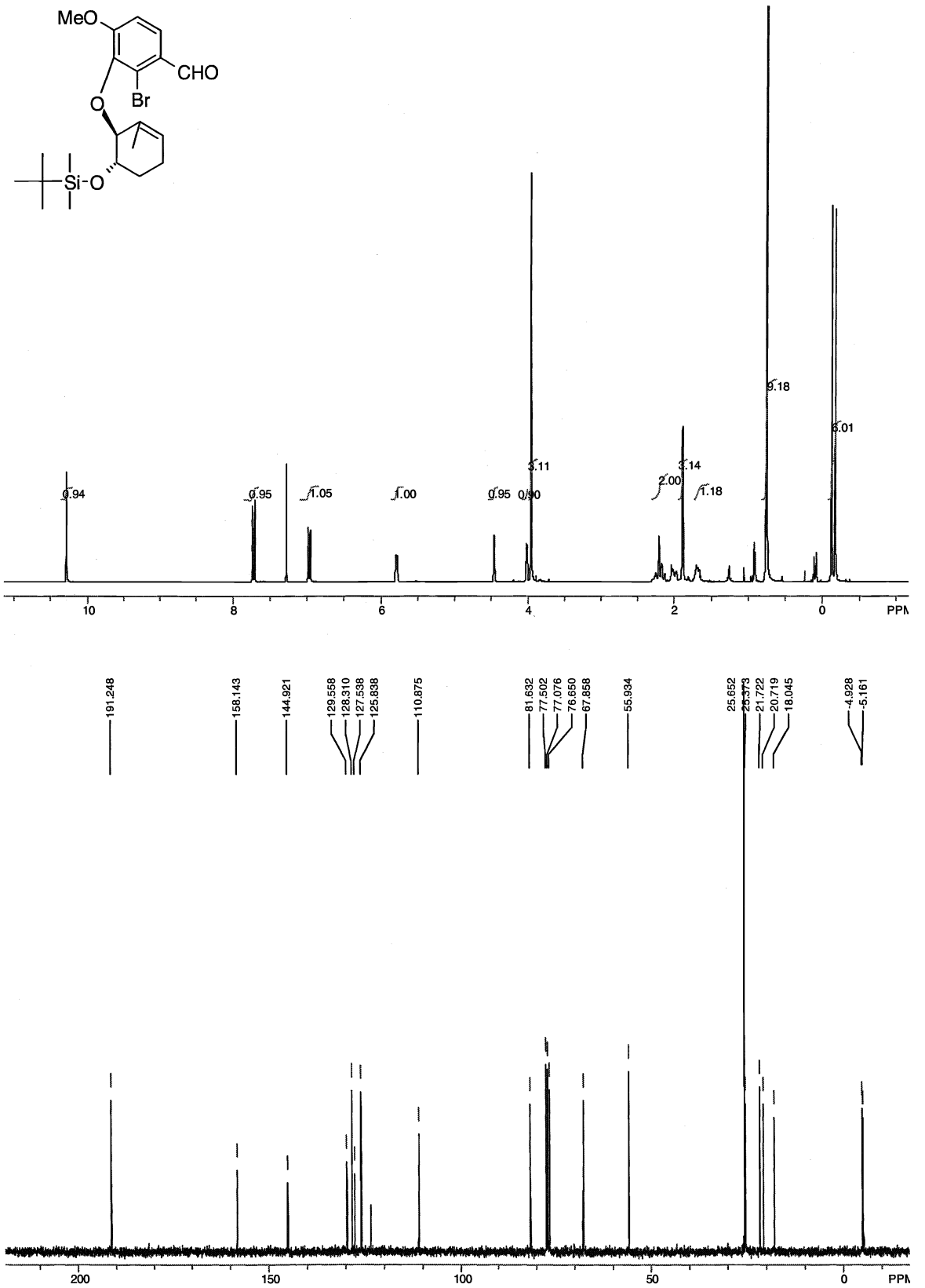
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Br
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Si-O
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3.14
1.18
9.18
6.01
10
8
6
4
2
0
PPM
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110.875
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77.076
76.650
67.858
55.934
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150
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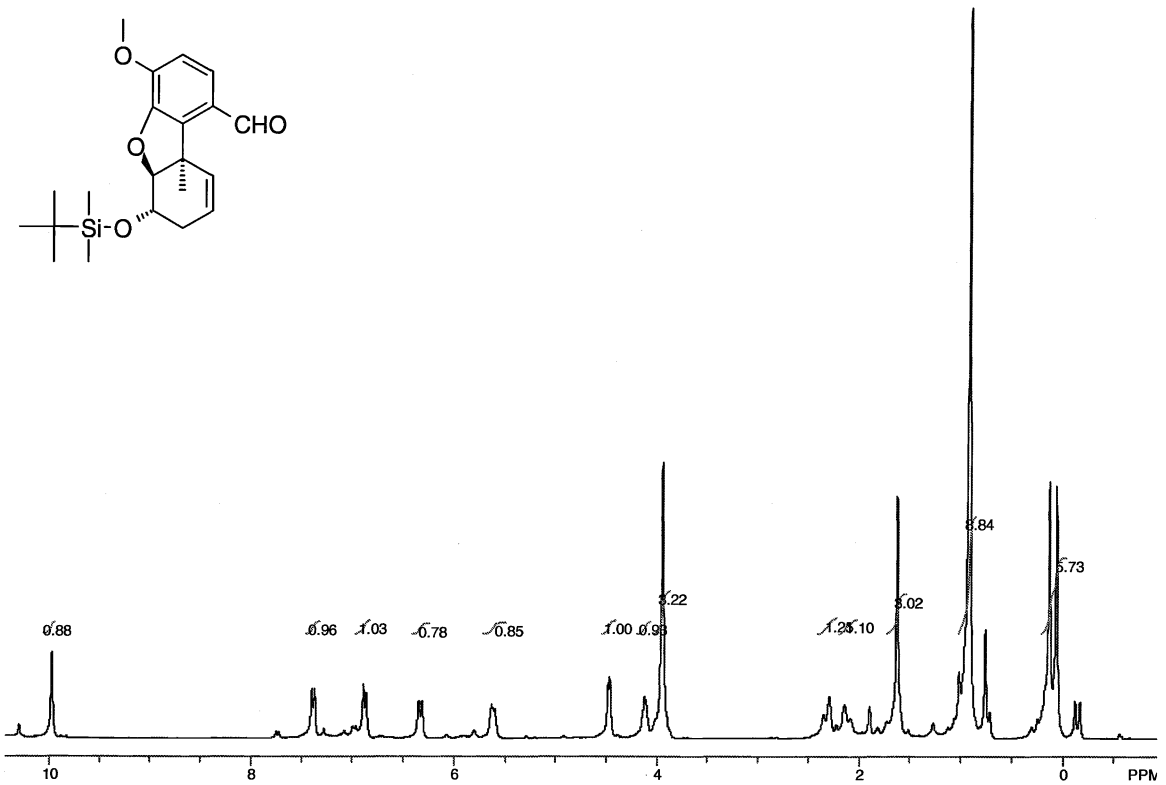
50
0
PPM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Si-O
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10
8
6
4
2
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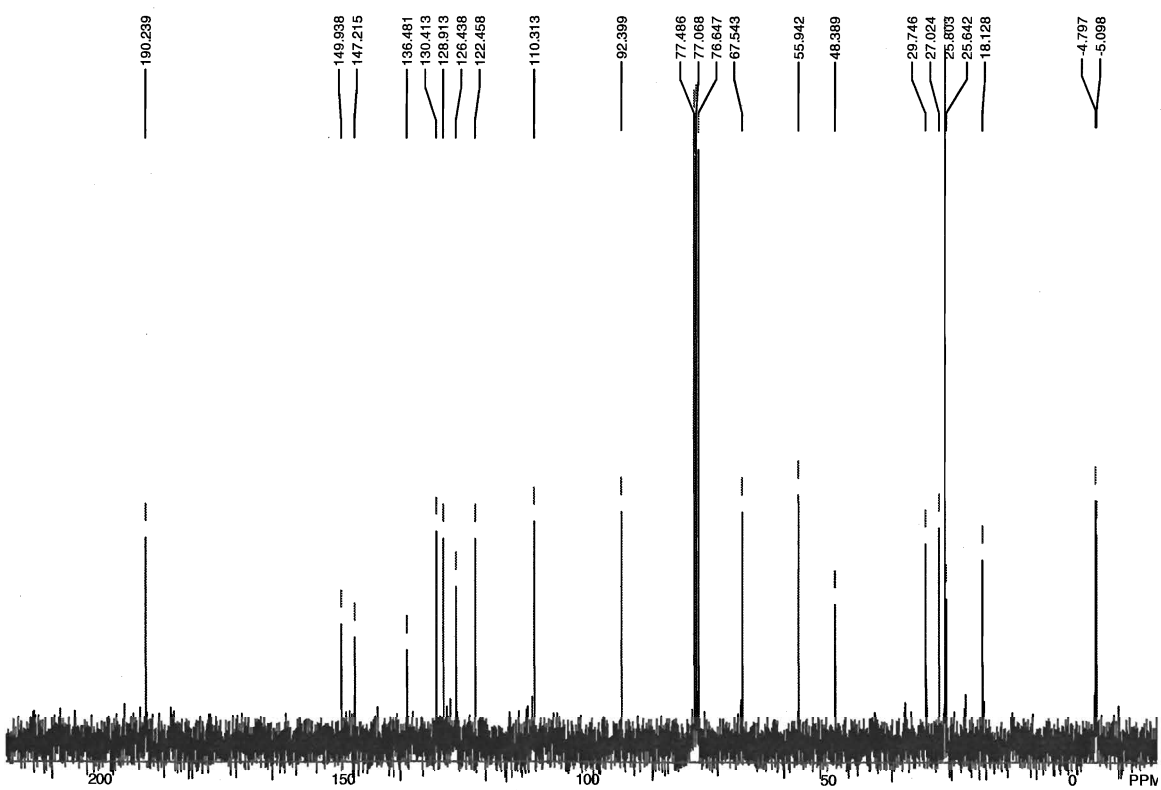
PPM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76.647
67.543
55.942
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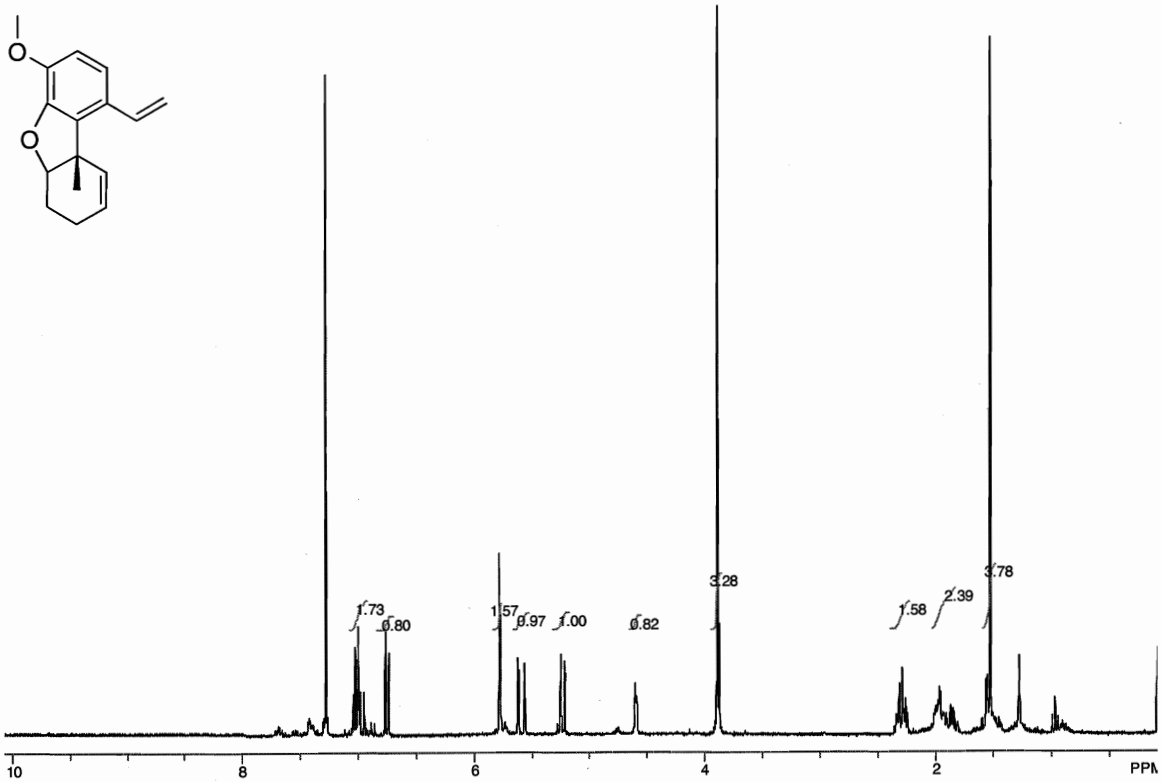
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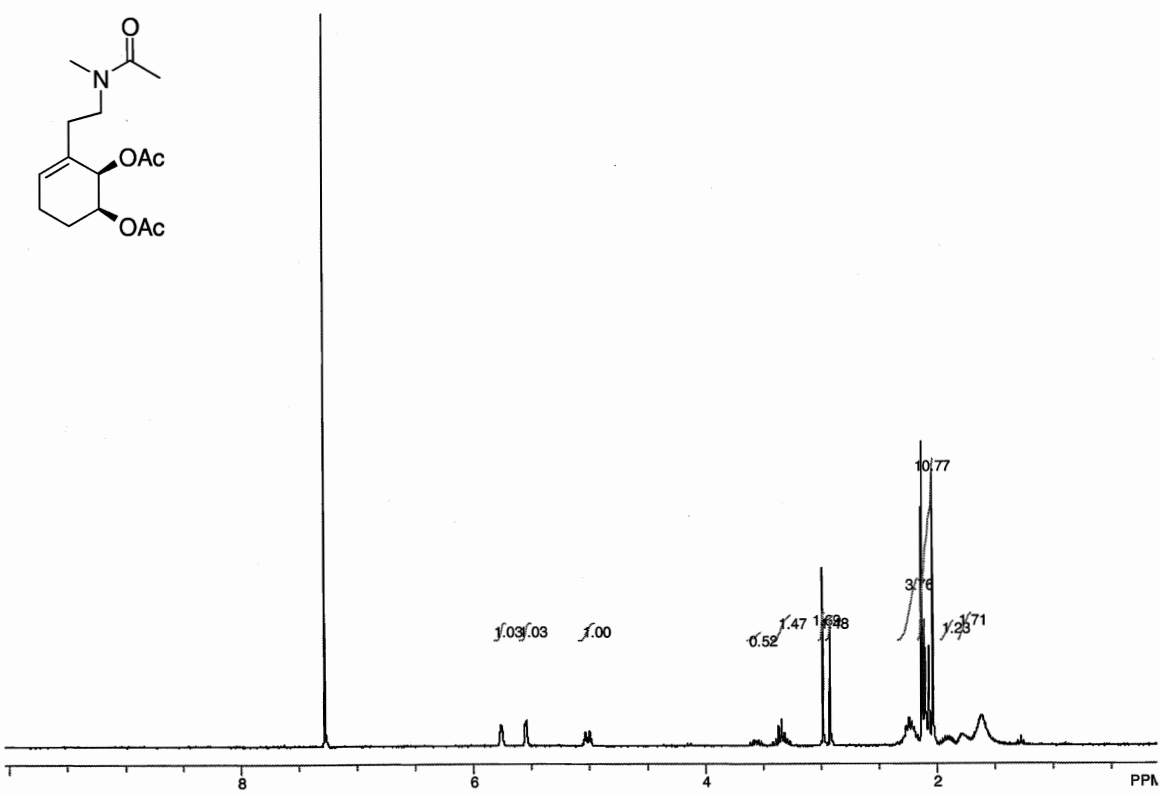
3.78
10
8
6
4
2
PPM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N
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OAc
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1.00
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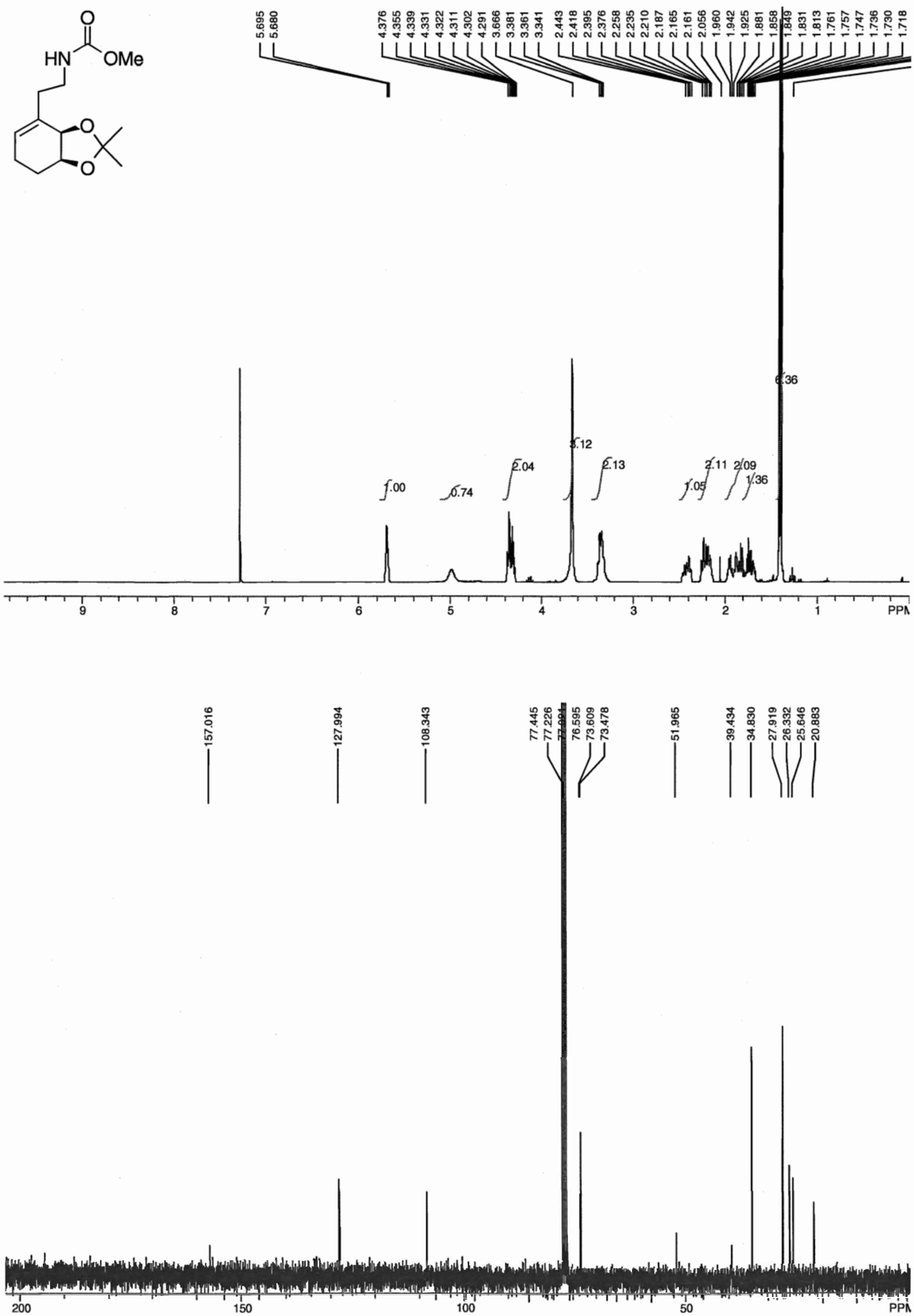
10.77
1.71
8
6
4
2
PPM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OMe
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O
O
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4.322
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4.291
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1.831
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1.761
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1.718
1.00
0.74
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3.12
2.13
1.05
2.11
2.09
1.36
6.36
9
8
7
6
5
4
3
2
1
PPM
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77.226
76.595
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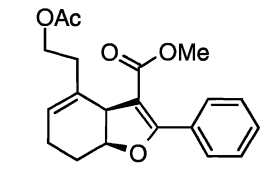
50
PPM


OAc
O
OMe
O

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1.00
1.00
1.0402
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3.35
2.02
0.83
1.00
8
7
6
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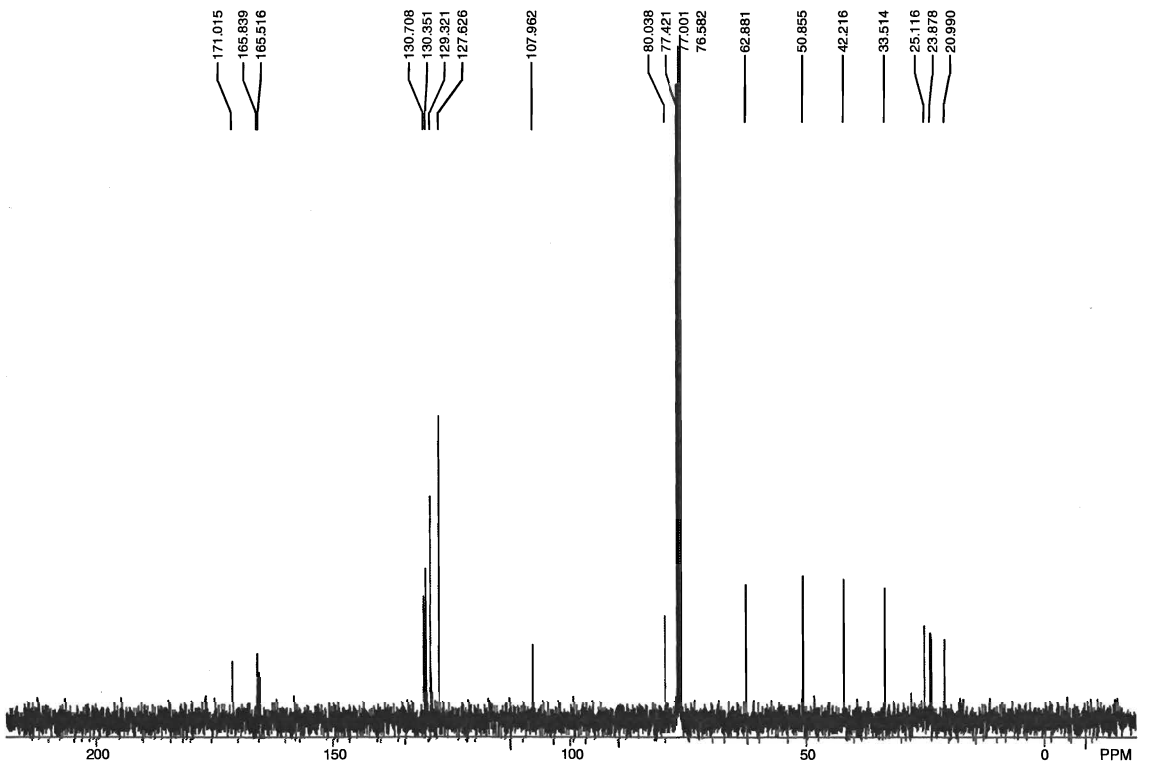
3
2
1
PPM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62.881
50.855
42.216
33.514
25.116
23.878
20.990
200
150
100
50
0
PPM

VII. Vita

Kevin J. Finn was born and raised in Hartville, Ohio, USA in 1978. He and his elder sister, Erin, were raised by their parents, James and Stella. He attended Lake High School, where his interest in chemistry was initially sparked by teacher, Mike Mihalik. After graduation in 1997, he studied chemistry at Ohio University and worked under the supervision of Professor Mark C. McMills in the area of transition metal-mediated carbenoid transformations. Finn graduated with honors in 2002 and moved to Gainesville, FL, USA to pursue graduate studies with Professor Tomas Hudlicky at The University of Florida. He spent one year at The University of Florida before moving to Brock University in St. Catharines, Ontario with Professor Hudlicky, who had been offered a prestigious Canada Research Chair Professorship. He is presently working toward completion of his PhD in Chemistry. His research interests include the isolation of new bacterial metabolites from microbial transformations with emphasis on application of these metabolites in asymmetric synthesis.

VIII. References

[1] Gibson, D.T. Koch, J.R.; Schuld, C.L.; Kallio, R.E. *Biochemistry* **1968**, *7*, 3795.

[2] Zylstra, G. J., Gibson, D. T., *J. Biol. Chem.*, **1989**, 264, 14940.

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